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Edited by David B. Paintin

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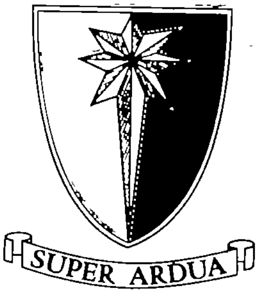

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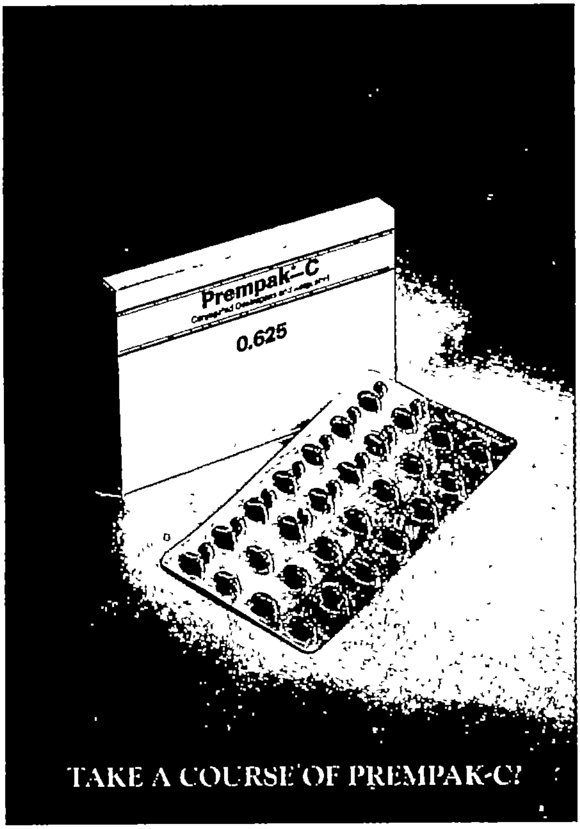

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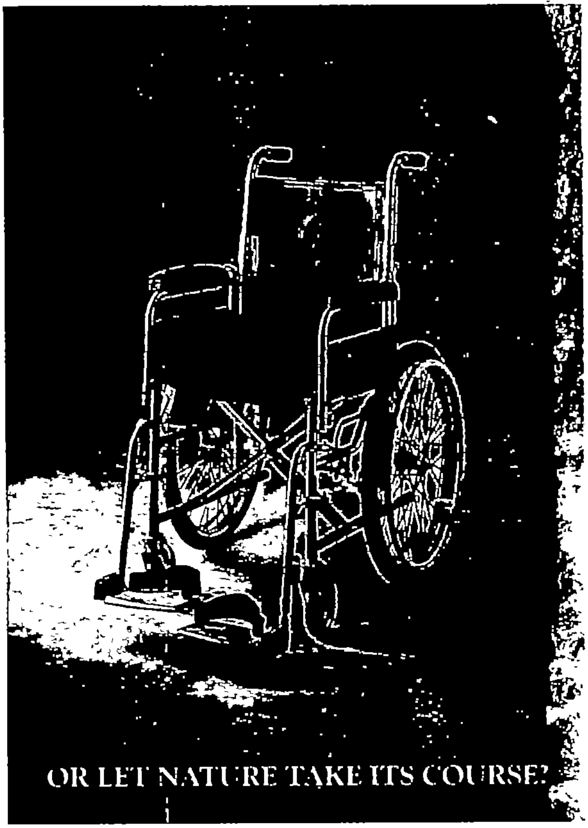

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The journal has published check lists to guide contributors preparing accounts of certain types of research. These appeared in 1989 (Vol 96). Bracken M. B., Reporting observational studies, 383–388, Wald N & Cuckle H, Reporting the assessment of screening and diagnostic tests, 389–396, Grant A, Reporting controlled trials, 397–400.

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COMMENTARIES

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External cephalic version at term: how high are the stakes?

It is perhaps a measure of the biological advantage of cephalic presentation to the human species that its natural predominance over breech presentation at term is by as much as 25 to 1. Persistence of breech presentation may reflect fetal or maternal disorders interfering with mechanisms which favour the cephalic presentation. In most cases, however, breech presentation appears to be a chance occurrence, or one related to an otherwise benign variant such as cornual placental position. Such a mishap places a healthy fetus and healthy mother at increased risk of complicated vaginal delivery or caesarean section. It is not surprising that the possibility of converting breech to cephalic presentations has, over the years, intrigued those involved with the care of pregnant women.

Prior to the 1970s, the use of external cephalic version (ECV) before term (usually at 30–34 weeks gestation) was widespread. Obstetricians who favoured or opposed the procedure often did so with quite peculiar fervour. Some proponents seemed to regard ECV as a test of their obstetric skill, and went to extraordinary lengths, including the use of general anaesthesia, to maintain unbroken records of success. Attitudes to ECV were aptly described by MacArthur (1964): 'There are those who enthusiastically recommend it, others who violently oppose it, and still others who express a rather elegant distaste for it.'

By the mid-1970s, the popularity of ECV before term was declining. There was uncertainty about the effectiveness of ECV at a gestational age at which spontaneous version occurs commonly, and there were reports of fetal mortality following ECV in the region of 1%. Furthermore, caesarean section was increasingly viewed as a safe alternative to vaginal breech delivery in unfavourable circumstances.

About the same time, Saling & Muller-Holve (1975) reported that ECV could be achieved in most breech pregnancies beyond 37 weeks gestation. Delaying ECV till term has several advantages: most spontaneous versions have occurred by 37 weeks gestation; other pregnancy complications have become evident; and in the event of complications of ECV, rapid delivery of a mature infant is feasible. The advent of ultrasound techniques and electronic fetal heart rate monitoring have made it possible to assess the pregnancy and confirm fetal wellbeing before and after the procedure with greater certainty than was possible previously. Furthermore, although tocolysis has been used routinely to facilitate ECV at term, as originally proposed by Saling & Muller-Holve (1975), it may be unnecessary in many pregnancies (Hofmeyr 1983; Robertson *et al.* 1987).

How effective is ECV at term? The report of Mohamed *et al.* in this issue of the Journal (pp. 8-13) is the fifth randomized control trial to show a considerable reduction in the incidence of breech birth and caesarean section, the typical odds ratios derived from the trials being 0·13 and 0·36 respectively (Hofmeyr 1990) (Tables 1 and 2). The higher rates of both ECV success and spontaneous version in the studies of black African women (Hofmeyr 1983; Mohamed *et al* 1990) are probably due to a tendency towards late engagement of the presenting part in the pelvis (Hofmeyr *et al* 1986). The effects of ECV in the United Kingdom would be expected to approximate those reported in the North American and European randomized trials: a reduction in the chance of breech birth from 78 to 44% and of caesarean section from 29 to 15% for those women in whom ECV is attempted.

The magnitude of the problem of breech presentation is illustrated by figures from the John Radcliffe Hospital, Oxford, where ECV at term with tocolysis is seldom used: Between 1986 and 1988, singleton breech delivery at ⩾ 37 weeks gestation occurred in 3·3% of all births. More than half of these babies were born by caesarean section, and these deliveries accounted for 18%

Table 1. Effect of external cephalic version at term on non-cephalic births

Study	Treated		Control		Odds ratio (95% CI)
	n	(%)	*n*	(%)	
Van Veelen *et al.* (1989)	39/89	(43·82)	67/90	(74·44)	0·28 (0·16–0·51)
Van Dorsten *et al.* (1981)	8/25	(32·00)	19/23	(82·61)	0·13 (0·04–0·41)
Hofmeyr (1983)	1/30	(3·33)	20/30	(66·67)	0·06 (0·02–0·19)
Mahomed *et al.* (1990)	18/103	(17·48)	87/105	(82·86)	0·07 (0·04–0·13)
Brocks *et al.* (1984)	17/31	(54·84)	29/34	(85·29)	0·23 (0·08–0·68)
Typical odds ratio					0·13 (0·10–0·19)

of all caesarean sections performed in the hospital (Redman & Yudkin, personal communication).

At the University of Mississippi Medical Center between 1982 and 1984, during which time ECV was attempted in 2·3% of pregnancies, vaginal breech deliveries decreased from 1·8 to 1·1% and breech caesarean sections from 2·8 to 1·6% compared with figures for the preceding 3 years (Morrison *et al.* 1986).

What are the implications of all these data for obstetrics in the United Kingdom? Using the most conservative estimates based on the randomized trials from North America and Europe, every 100 ECV attempts should prevent 34 breech births and 14 caesarean sections. If ECV at term were attempted in only 2% of the 750 000 pregnancies in the United Kingdom each year, these 15 000 ECV attempts should reduce the number of breech births by 5100 and the number of caesarean sections by 2100.

What are the relative risks and benefits of ECV at term? For the fetus, the risk of ECV at term in the context of current obstetric care seems very small indeed. In a review of 979 reported cases of ECV at term with neither general anaesthesia nor inhalational analgesia, there were no fetal losses (Hofmeyr 1989). Against any risk of ECV to the fetus must be weighed the risks of persistent breech presentation after 37 weeks gestation. In addition to the risks of vaginal breech delivery, even when caesarean section is intended to avoid such risks, there are dangers in persistent breech presentations in the form of precipitous delivery before arrival in hospital, or rupture of membranes with cord prolapse. Caesarean section does not eliminate birth trauma in breech presentations (Tatum *et al.* 1985), and may increase the risks of pulmonary hypertension in the newborn (Heritage *et al.* 1985).

For mothers, the benefits are more clearly defined. ECV is a minor procedure, though the possibility of negative psychological effects for mother and caregivers when it fails has been raised (Keirse, personal communication). It results in a considerable reduction in the risks both of caesarean section and of vaginal breech delivery, which often entails an operative delivery with forceps and episiotomy (Tatum *et al.* 1985). Maternal morbidity is higher after caesarean section than after vaginal delivery (Tatum *et al.* 1985; Miller 1988). Indeed, it should not be forgotten that, although the operation has become safer, it is still associated with a four times higher maternal death rate than is vaginal delivery in England and Wales (Department of Health 1989). Reproductive function

Table 2. Effect of external cephalic version at term on caesarean section

Study	Treated		Control		Odds ratio (95% CI)
	n	(%)	*n*	(%)	
Van Veelen *et al.* (1989)	8/89	(8·99)	13/90	(14·44)	0·59 (0·24–1·47)
Van Dorsten *et al.* (1981)	7/25	(28·00)	17/23	(73·91)	0·17 (0·05–0·51)
Hofmeyr (1983)	6/30	(20·00)	13/30	(43·33)	0·35 (0·12–1·02)
Mahomed *et al.* (1990)	13/103	(12·62)	35/105	(33·33)	0·31 (0·16–0·60)
Brocks *et al.* (1984)	7/31	(22·58)	12/34	(35·29)	0·55 (0·19–1·58)
Typical odds ratio					0·36 (0·24–0·54)

following caesarean section is compromised (Hemminki 1987) and there may also be negative emotional effects on the mother and her relationship with her baby (Garel *et al.* 1990).

The randomized trials of ECV at term reported so far have demonstrated unambiguously that the procedure reduces breech births and caesarean sections. They have not been large enough to define the relative risks to the fetus, though the evidence available is in favour of ECV. This leaves two reasonable options for the management of uncomplicated breech presentation at term: either routine use of ECV at term, or participation in further, larger randomized trials designed to compare fetal and maternal morbidity with and without ECV at term. An attitude of 'elegant distaste' is no longer tenable.

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The treatment of CIN: do we need lasers?

Women with abnormal cervical cytology constitute a large proportion of gynaecological referrals in the United Kingdom (21% in this unit). The management of these patients has altered dramatically in the last 30 years, mainly due to the introduction of colposcopy. Treatment of cervical intraepithelial neoplasia (CIN) has become increasingly more conservative. Hysterectomy was replaced by large cone biopsy, which in turn has been largely superseded by local destructive therapy.

Colposcopy has allowed women with abnormal cytology to be assessed individually. Two basic groups of patients with CIN are identified. Those requiring a cone biopsy and those suitable for local destructive treatment. Patients with either a suspicion of invasive disease, a glandular abnormality, or an unsatisfactory colposcopy must be treated by cone biopsy. When the whole of the transformation zone is visible a directed biopsy should provide a representative histological diagnosis and allow treatment by local destruction of the epithelium.

Local destruction

Diathermy, cryosurgery, cold coagulation, and the carbon dioxide laser have all been extensively used for the local destruction of CIN. As this epithelial abnormality may involve the gland crypts in the transformation zone, all local destructive methods must destroy the underlying cervical stroma to at least 5 mm to be effective. For those methods where the depth can be measured a minimum of 7 mm is recommended. Each method of local destruction has its own entrenched supporters who can achieve one treatment success rates of approximately 95% with minimal complications (Giles 1988). Long-term follow-up of all these methods has not shown any significant effect on either fertility or pregnancy. Most patients in the United Kingdom are now treated by either laser therapy or cold coagulation (I. D. Duncan, personal communication). Diathermy and cryotherapy have become increasingly less popular as diathermy requires a general anaesthetic and cryotherapy has a variable success rate.

Laser protagonists argue that the accuracy of treatment and lack of scarring more than compensates for the prohibitive cost of the equipment. However Gordon & Duncan in this issue of the Journal (p. 14) again demonstrate the effectiveness of the cold coagulator in a large series of patients with CIN 3. This almost certainly results in less tissue loss than laser vapourization but is equally as effective. Earlier criticism of their method of follow-up, namely that it relies on cytology alone, has now been shown to be invalid. Two recent studies (Giles *et al.* 1989; Lopes *et al.* 1990) show no benefit of routine post-treatment colposcopic examination and found frequent cytology to be as effective.

As cold coagulation is technically easier, quicker to use, and considerably cheaper it must be considered the treatment of choice for the local destruction of CIN.

Local excision as an alternative to destruction

Concern over the inability of colposcopy and directed biopsy to distinguish reliably microinvasion from CIN 3 has led to calls for the excision rather than destruction of CIN (Grundsell *et al.* 1983).

Formal knife cone biopsy under general anaesthesia is the traditional method of excising CIN. The procedure involves removing the transformation zone as a cylinder to a depth indicated by prior colposcopic examination. When there is no evidence of endocervical disease, the depth of excision need be no more than 8 mm.

Laser can be used to excise the transformation zone as a shallow cone biopsy, often using only local anaesthesia. This allows further histological assessment (Baggish 1986; Partington *et al.* 1989; McIndoe *et al.* 1989). Earlier claims of minimal artifactual damage to the specimen are now being questioned. In practice, it is the smaller laser excisions that become dessicated. This leads to the temptation to remove more tissue with a laser than one would have vaporized. Laser excisions attempt to remove a cylinder of tissue to a depth of 8–10 mm (Partington *et al.* 1989; McIndoe *et al.* 1989). However, the average depth of excision in most series is in excess of this. Such deep excisions are unnecessary where lesions are suitable for local destruction and perhaps reflect the difficulties in assessing depth with this technique.

The introduction of large loop excision of the transformation zone (LLETZ) by Prenderville *et al.* (1989) offered a new method of outpatient excisional biopsy. Various size diathermy loops allow virtually any transformation zone to be removed with local anaesthesia. The technique is easier than laser excision and is considerably quicker. The excised tissue is suitable for histological examination, but both methods cause heat artefact in the specimen and this may cause problems. There is no difference in the complication rate. The cost of the equipment necessary is considerably less than that required for laser excision, and it does not require expensive maintenance. Early results are promising but lack of long-term data on cervical function make claims for LLETZ to be the ideal choice for the treatment of CIN premature The short-term advantages of LLETZ over the laser vaporization have been described by Gunesekera *et al.* (1990).

As the diagnosis of microinvasive carcinoma can only be made after a cone biopsy the unit in Dundee (Gordon & Duncan 1990) are obviously treating many more microinvasive lesions than their results, which are based on small colposcopic biopsies, suggest. However, their treatment is effective and the risks of inadvertantly treating these colposcopically unsuspected lesions by local destruction seems to be more theoretical than actual.

The see and treat policy of the unit in Dundee inevitably involves some women being treated with cold coagulation when this is not appropriate. The introduction of excisional methods has encouraged other units to embark on similar policies involving treatment at the first consultation. Luesley *et al.* (1990) have reported the results of a 'see and loop' approach to colposcopy. The early treatment success is excellent but over 25% of patients treated had no histological evidence of CIN. Such over-treatment is unacceptable when the long term effects on fertility and pregnancy are unknown. To recommend excision of the transformation zone for all coposcopy referrals is a retrograde step. This is basically resorting to the old practice of mandatory cone biopsy (albeit colposcopically controlled). The inevitable excessive destruction of normal tissue is to be deplored.

Before advocating local excision for all CIN, large-scale studies comparing not only treatment success but also long term morbidity are required.

Alternatives to knife cone

A cone biopsy is required to remove the appropriate depth of cervical canal when there is evidence of endocervical disease. Some units are using the laser or the diathermy loop to perform such cone biopsies. Clinicians should be aware that the heat artifact may make the subsequent histological interpretation difficult.

It is time for a rational reappraisal of the treatment of CIN. The aims of the colposcopist must be to prevent the development of invasive disease, and to return the cervical cytology to normal with the minimum of physical and psychological morbidity. Despite the logistical attractions of a 'see and treat' policy, we believe that patients deserve a diagnosis before embarking on treatment.

Medicine is increasingly cost conscious. Lasers are expensive and have no advantages over cheaper alternatives. There is no doubt in our minds that CIN lesions suitable for local destruction are best treated with the Semm cold coagulator. When dealing with the colposcopically higher grade lesions the colposcopist should exercise caution and excise the transformation zone. Most can be adequately treated with the diathermy loop in out-patients.

Laser surgery is exciting and has an enormous future in all specialities but should no longer be considered essential, or even necessary, for the best treatment of CIN.

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What constitutes an adequate cervical smear?

Before asking a woman to offer herself for a screening test it must be certain that the test will either lead to the prevention of the disease or, if detected early, give her a better chance of cure. Population screening programmes that are systematic and comprehensive, as in Scandinavian countries, Iceland, British Columbia and some areas of Scotland, have been effective in lowering both the occurrence and the mortality from carcinoma of the cervix. Screening programmes can be effective only if women have adequate smears taken—a smear that accurately reflects the underlying histology. It is amazing that 30 years after cervical screening began in this country, the question 'What constitutes an adequate smear' is still being asked.

Recently there has been a tendency to judge a cervical smear by the presence or absence of endocervical cells. The presence of these cells indicates that the cervix has been seen, but smears taken from up the canal by spatula or brush can be composed almost entirely of endocervical cells and may be useless for detecting a preinvasive cancer in the transformation zone. Endocervical cells are relatively easily obtained in young women in whom the squamo-columnar junction is often on the ectocervix, but are much less accessible to a spatula in post-menopausal women, in whom the junction may be inside a narrow cervical canal. Beilby *et al.* (1981) found that the presence of endocervical cells did not improve the detection rate of cervical dysplasia. They observed better detection rates when two smears were taken at one visit but this is impractical in an already overloaded system.

The presence of endocervical cells provides a useful criterion of a properly taken smear. Woodman *et al.* (1989) looked at the association between negative smears and the presence or absence of endocervical and immature metaplastic cells by comparing positive smears with negative smears from the same woman. They found that negative smears were less likely to contain endocervical cells than dyskaryotic smears, but this association was not statistically significant. Voojs *et al.* (1985), in Holland, screened 30 055 women a second time after three years and found an increased rate of dyskaryosis in smears with endocervical cells.

In an effort to obtain endocervical cells more easily, various types of spatulas have been designed. The Aylesbury spatula, which has been generally adopted, was tested against the Ayre spatula in a study of 17 000 smears by Wolfendale *et al.* (1987). A better cell content and 22% more smears showing dyskaryosis were obtained with the Aylesbury spatula. In this issue of the Journal Woodman *et al.* (page 21) describe a controlled trial comparing the sampling efficacy of the Ayre and Rocket spatulas. Smears taken with the Rocket spatula were more likely to contain endocervical cells and less likely to contain immature metaplastic cells but both spatulas yielded a similar proportion of smears containing dyskaryotic cells. The detection rate of abnormal cells is the best measure of sampling efficiency and endocervical and immature metaplastic cells do no more than provide evidence that the spatula has sampled the endocervix.

An adequate smear will contain cells from the whole of the transformation zone and may include endocervical cells and immature metaplastic cells. Microscopically, however, immature metaplastic cells are not always recognizable. Ideally these cells will be present and recognized but an adequate sample must contain large numbers of epithelial cells in a good state of preservation obtained from a 360° sweep of the cervical surface. Small lesions are those most frequently missed (Giles *et al.* 1988).

The type of spatula may make some difference but the hand that wields the spatula is of paramount importance. Training in smear-taking is simple, but those who take smears are not always adequately trained. More is required if inadequate cell samples are to be avoided. Passing the speculum is not too difficult but finding the cervix requires a little practice. Few medical students become really proficient at smear taking and, on becoming general practitioners, have to acquire skill from practical experience, aided only by occasional comments on the report forms such as 'inadequate smear—please repeat'. It is in this context that the presence of endocervical and immature metaplastic cells may be used as a relevant criterion of efficiency.

Should nurses take smears? With a target, to screen 80% of women in their care between 20–64 years of age, many general practitioners will delegate the taking of smears to their nurse. Many take better smears than some doctors but some nurses do not always see the cervix and may settle for a flap of vaginal wall. If they have difficulty they can call the doctor from his consulting room next door but if their next client is also difficult, will they ask the doctor to help again? Nurses are not trained to pass a speculum or to take cervical smears and do not have a medical student's training on the appearance of the cervix. Identifying an invasive cancer by looking at the cervix is not always easy for a gynaecologist, far less for a nurse. It is not sufficiently appreciated that invasive cancers may give negative or inadequate blood-stained smears.

The British Society of Clinical Cytology published a successful booklet in 1981 with suggestions for taking an adequate smear and showing the cell types expected on the slide. In 1988 the Society launched a useful video titled 'Taking Cervical Smears' and some of the funding for this project from the Department of Health was conditional on the approval of the nursing profession. Training in smear taking should be a brief but important part of the medical undergraduate curriculum. If nurses are to take smears they should receive formal training and obtain a certificate. A screening test must do more good than harm. A negative smear can give a sense of false security.

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External cephalic version at term. A randomized controlled trial using tocolysis

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Abstract

Objective—To assess the role of external cephalic version (ECV) at term, using tocolysis.
Design—A randomized controlled trial over a 12 month period.
Setting—Harare Maternity Hospital, Harare, Zimbabwe.
Subjects—208 women with breech presentation at term were recruited after satisfying eligibility criteria. There were 103 women in the study group and 105 in the control group. At the end of the study a further 104 women were recruited for ECV.
Intervention—ECV attempted after intravenous injection of 10 μg of hexaprenaline, using either forward or backward somersault over a maximum period of 5 min.
Main outcome measures—Success rate in terms of presentation during labour, need for caesarean section, and various variables related to fetal outcome.
Results—ECV reduced the frequency of breech presentation during labour from 83% to 17% and that of caesarean section from 33% to 13%. There were no troublesome complications from the procedure.
Conclusion—In carefully selected women with breech presentation, ECV at term using tocolysis, safely reduced the rate of breech presentation in labour and also the caesarean section rate. Further research is needed to determine the role of ECV in early labour.

The management of breech presentation before and during labour remains controversial.

Several studies (Collea *et al.* 1980; Green *et al.* 1982; Mahomed 1988) have found no difference in perinatal outcome after vaginal breech delivery in carefully selected pregnancies. This has, however, not been a universal finding. In our own unit, a recent case-control study (Mahomed *et al.* 1990) showed that the perinatal mortality rate (7% *vs* 1·6%), the admission rate for neonatal intensive care (25% *vs* 10%) and the frequency of low Apgar scores (6% *vs* 0·5%) were all higher after vaginal delivery. In our experience, therefore, reducing the occurrence of breech presentation during labour would be desirable.

The use of external cephalic version (ECV) has been reviewed by Savona-Ventura (1986) and by Hofmeyr (1989). Three randomized controlled trials have failed to demonstrate any beneficial effect of ECV before term (Hofmeyr 1989). There is some consistency with regard to studies of ECV at term. Pooled data from three randomized trials showed that the frequency of cephalic delivery was increased and that of caesarean section significantly reduced.

The aim of the present study was to assess the role of ECV at term using tocolysis in our own unit where, as a result of a previous study of ECV before term (Kasule *et al.* 1985), ECV had almost been abandoned.

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Subjects and methods

This was a randomized controlled trial of ECV after 37 weeks gestation with the use of tocolysis. The hypotheses were that ECV would reduce the frequency of breech presentation in labour and also the need for abdominal delivery. All women with singleton breech presentation at ≥37 weeks gestation, seen for antenatal care at Harare Maternity Hospital, Harare, Zimbabwe, were eligible for recruitment. The gestational age was calculated from the date of the last normal menstrual period and confirmed by ultrasound scan if there was a discrepancy of >2 weeks between gestation by dates and by palpation. Those with a history of antepartum haemorrhage, placenta praevia, uterine scar, severe proteinuric hypertension, diabetes, cardiac disease or ruptured membranes were excluded from the study. After an ultrasound scan, a non-stressed cardiotocogram was recorded. Only women with fetuses showing a reactive pattern or a normal baseline rate with good variability and no decelerations were eligible for final recruitment. Consecutive women were then allocated to ECV or the control group using consecutively numbered sealed opaque envelopes. Recruitment continued until the sample size of 100 women per group was reached. The sample size had the power to demonstrate a reduction in breech presentation from 80% to 30% with 95% certainty. Randomization was performed using a block size of six. Informed consent was obtained from all women before recruitment. No woman refused to enter the study. The study was approved by the departmental board.

All women were seen weekly for routine antenatal care until delivery. When the fetus continued to present by the breech, a decision was made about the best method of delivery by the responsible consultant on the basis of the guidelines used within the department.

ECV was conducted by requesting the woman to lie with a slight lateral tilt. A Kleihauer Betke test was performed before and immediately after the procedure. Each woman received 10 μg of hexaprenaline (Ipradol) injected intravenously over 1 min and version was then attempted using either a forward or a backward somersault, as described previously (Hofmeyr 1983). Version was attempted over a maximum period of 5 min. At the end of the procedure the cardiotocogram was repeated. Most of the versions (85%) were performed by KM.

The following maternal and fetal variables were examined in the experimental group. (i) Frequency of cephalic presentation during labour (ii) Ease of version defined according to the time required to complete the version, and also as being easy, moderately difficult or very difficult, as judged by the clinician. (iii) The woman's discomfort during the procedure (described subjectively as painless, mildly, moderately or very painful). (iv) Fetal heart rate abnormality during and immediately after the procedure. (v) Time of onset of labour after enrolment. (vi) Mode of delivery. (vii) Apgar scores, admission to neonatal unit, stillbirth and neonatal death.

Variables i, v, vi and vii were also assessed in the control group. The assessors of the outcome variables listed under (vii) above did not know whether the subject was in the study or the control group.

The data were analysed using the Statistical Package for Social Sciences. Categorical variables were analysed with the χ^2-test and continuous variable with Student's *t*-test; $P<0\cdot05$ was considered statistically significant. Outcome variables were compared using relative risks with 95% confidence intervals (CI). There were no withdrawals or losses to follow-up after enrolment.

Results

During the period February 1987 to March 1988, 208 women were recruited into the study. In April 1988 the control arm was abandoned in an effort to address the issue of safety of the procedure. A further 104 women were recruited for ECV up to September 1988. Maternal and fetal characteristics are shown in Tables 1 and 2. Randomization achieved a satisfactory balance in descriptive variables. In particular there were comparable numbers of primigravidae and the type of breech in each group. Fundal placentas occurred more often in the ECV group.

Version was attempted in 103 women in the ECV group and was successful in 89 (86%); 85 (83%) presented by the vertex during labour and four fetuses (3%) reverted spontaneously to a breech presentation. Of the 105 women in the control group 18 (17%) presented by the vertex during labour. The difference between the two groups was highly significant ($P<0\cdot001$).

Maternal complications

No serious maternal complications attributable

Table 1. Maternal characteristics in the study and control groups

	Study group (n = 103)	Control group (n = 105)
Maternal age (years)		
Mean (SD)	26·6 (6·6)	26·7 (6·6)
<16 years	3 (3%)	1 (1%)
Parity		
Mean (SD)	2·0 (1·8)	2·4 (2·0)
Primigravida	27 (26%)	25 (24%)
Parity >3	41 (40%)	47 (45%)
Maternal height (cm)		
Mean (SD)	156 (7) (n = 89)	159 (8·4) (n = 92)
<150 cm	19 (21%)	14 (15%)
Booking weight (kg)		
Mean (SD)	66 (11) (n = 89)	66 (12) (n = 92)
>85 kg	4 (4%)	6 (7%)

to version were noted. There were no instances of antepartum haemorrhage or uterine rupture. One woman complained of sweating and feeling faint as a result of hypotension from the hexaprenaline, and three women had troublesome palpitations for up to 1 h. More women in the ECV group went into labour within 24 h of enrolment (7% compared with 3%) (Table 3). The rate of caesarean section in the ECV group was 13% compared with 33% in the control group, and this difference was highly significant (RR 0·31, 95% CI 0·16–0.60). The overall caesarean section rate in those with breech presentation in labour was 39%. If only the primigravidae are considered, 19% of those with cephalic presentation compared with 68% of those with breech presentation required delivery by caesarean section (P<0·001).

Fetal complications

Two fetuses demonstrated a transient bradycardia but in both there was spontaneous recovery within 10 min and the rate always remained above 100 beats/min. Depressed neonatal state, defined by a 5-min Apgar score of ⩽5, occurred in 1% in the study group and in 2% in the control group. There were, however, no differences between the two groups in the number of infants admitted to the neonatal unit. If, however, primigravidae are analysed separately, 10% of the study group compared with 37% of the control group were admitted to the neonatal unit. There were 13 and 54 vaginal breech deliveries in the study and the control group respectively. The numbers were too small to compare complications, but in the study group, four infants were admitted to the neonatal unit purely for observation despite Apgar scores of >5, whereas in the control group, two babies had Apgar scores of ⩽5 and were admitted to the neonatal unit and the two deaths reported in the control group were vaginal breech deliveries.

There were three perinatal deaths; two occurred in the control group. One was in a woman with breech presentation who was scheduled for vaginal breech delivery, she arrived in labour 21 days after entry and had an assisted breech delivery 6 h after the onset of labour. The labour chart showed early decelerations with good recovery for an hour before delivery but the infant was born with Apgar scores of 1 and 1 at 1 and 5 min, respectively, and could not be resuscitated. The second death was in a woman who arrived at the hospital with the baby who had been born vaginally as a breech. Apparently there had been some delay in the birth of the head. All attempts at resuscitation were unsuccessful. As the birth occurred on the way from home no further details were available.

The perinatal death in the ECV group was a baby born 23 days after a successful version by an uncomplicated vaginal vertex delivery but the

Table 2. Fetoplacental characteristics in the two groups

	Study group (n = 103) n (%)	Control group (n = 105) n (%)
Gestation at recruitment (weeks)		
37	52 (50%)	46 (44%)
38	32 (31%)	32 (30%)
39	15 (15%)	17 (16%)
⩾40	4 (4%)	10 (10%)
Mean (SD)	38 (1)	38 (1)
Placental site		
Anterior	27 (26%)	30 (29%)
Posterior	23 (22%)	38 (36%)
Fundal	53 (52%)	37 (35%)
Position of fetal back		
Left	49 (48%)	52 (49%)
Right	43 (42%)	42 (40%)
Anterior	7 (6%)	9 (9%)
Posterior	4 (4%)	2 (2%)
Type of breech		
Frank	39 (38%)	37 (35%)
Flexed	64 (62%)	68 (65%)

Table 3. Comparison of outcomes in the two groups.

Variable	Study group (*n* = 103)	Control group (*n* = 105)	RR (95% CI)
Enrolment-labour interval (days)			
Mean (SD)	14 (11)	14 (9)	—
<1	7 (7%)	3 (3%)	2·4 (0·7–8·1)
2–7	26 (26%)	24 (23%)	1·1 (0·6–2·3)
>7 days	70 (68%)	78 (74%)	0·7 (0·4–1·5)
Gestation at delivery (weeks)			
Mean (SD)	39·9 (2)	39·9 (2·3)	—
>42 weeks	7 (7%)	6 (5%)	1·2 (0·4–3·2)
Breech presentation in labour	18 (17%)	87 (83%)	0·07 (0·04–0·13)
Caesarean sections	13 (13%)	35 (33%)	0·31 (0·16–0·60)
Apgar score at 5 min			
<7	8 (8%)	10 (10%)	0·8 (0·3–2·1)
≤5	1 (1%)	2 (2%)	0·5 (0·05–5·3)
NNU admission	18 (17%)	19 (18%)	0·96 (0·5–1·3)
Perinatal deaths	1	2	—

NNU = neonatal unit, RR (95% CI) = relative risk (95% confidence interval).

baby was very asphyxiated and died in the neonatal unit at 3 days of age, the CTG before ECV was unremarkable and the CTG after version was too short to demonstrate any variable decelerations.

Factors related to the ECV procedure

The 103 women in the ECV group and a subsequent consecutive series of 104 women with breech presentation and suitable for ECV comprise a total of 207 women who were treated with ECV. Not all these women had a scan immediately before the ECV and data are not available on all deliveries. However, factors related to the procedure are shown in Table 4. Over 55% of the versions were successful within 1 min and only 15% required up to 5 min. Of the 207 versions 73% were deemed easy and about 90% of the women experienced little or no discomfort during the procedure. ECV was statistically significantly more successful in parous women than

Table 4. Factors related to external cephalic version in 207 women

No. of women	207
Procedure immediately successful	180 (87%)
Time required (min)	
<1	114 (55%)
1–5	68 (33%)
>5	25 (12%)
Difficulty of procedure	
Easy	151 (73%)
Moderately difficult	52 (25%)
Very difficult	4 (2%)
Discomfort	
Nil	122 (59%)
Mild	58 (28%)
Moderate	27 (13%)
Abnormal fetal heart rate	2 (1%)
Final success rate	176 (85%)

Table 5. Factors related to success of external cephalic version in 207 women

Factor	Success rate
Parity	
Primigravida	40/53 (75%)*
Parity >3	72/81 (89%)*
Gestational age (weeks)	
37	92/107 (86%)
38	51/57 (89%)
39	29/33 (88%)
≥40	8/10 (80%)
Site of placenta	
Anterior	38/44 (86%)
Posterior	25/30 (83%)
Fundal	56/64 (88%)
Position of baby's back	
Left	59/73 (81%)
Right	51/57 (89%)
Anterior	7/7 (100%)
Posterior	2/2 (100%)
Type of breech	
Frank	47/60 (78%)
Flexed	40/45 (89%)

*$P<0·05$

in primigravide and the success rate was higher in those with a flexed breech than a frank one but the difference was not statistically significant (Table 5). Success did not appear to be related to gestational age, site of the placenta, or the position of the fetal back. There was one stillbirth in the 104 women who had an ECV but who were not randomized. The infant was born 17 days after successful version. Labour and delivery were uncomplicated but the infant was stillborn with the cord tightly around the neck.

Discussion

The results of this controlled trial clearly demonstrate that ECV using tocolysis at term in appropriately selected women reduces the occurrence of breech presentation in labour. The reported success rate for version after 37 weeks has varied from 8 to 97% (Savona-Ventura 1986). Our final success rate of 83% is substantially higher than that reported by some others (Van Dorsten *et al* 1981; Brocks *et al.* 1984; Ferguson *et al.* 1987; Marchick 1988; Morrisen *et al.* 1986). There are several possible explanations for this difference. Parity has an influence on the success rate, which is generally higher in multigravidae. Brocks *et al.* (1984) reported an overall success rate of 41%, but a rate of 62% in parous women. Similarly Van Dorsten *et al.* (1981) noted a lower success rate in nulliparous than in parous women, 37% compared with 65%. The different number of primigravidae in different studies may explain the differing success rates. In our study 26% were primigravida compared with 68% and 60% in the series described by Brocks *et al.* (1984) and Marchick (1988) respectively.

Whilst some authors have noted success rate to be affected by gestation (Van Dorsten *et al* 1981), our success rate did not seem to be related to gestation. Similarly, experience is said to affect success of ECV (Savona-Ventura 1986). None of the investigators in this study had had much previous experience with ECV and yet our success rates for the first 25 women (82%) was not significantly different from that for the last 25 (85%). Others have also noted similar experience and this probably suggests that under tocolysis these factors may not play as important a role as has been suggested

Ferguson *et al.* (1987) noted that version rates were reduced if a major portion of the placenta was localized in the cornua, but in pregnancies with non-cornual placentas, success rates were similar. Fianu & Vaclavinkova (1979) also concluded that success rates were better for anterior and posterior placentas than for fundal or cornual ones. Our results did not show any difference, although cornual locations were not categorized separately. It has been suggested that the site of the placenta probably alters the intrauterine configuration and lessens the available space for forward roll or backward flip (Ferguson *et al.* 1987). The type of breech has also been noted to affect version. Whilst some previous investigators found that extension of the fetal legs did not influence success of ECV (Bradley-Watson 1975; Ellis 1968), we noted a slightly lower success rate with frank than with flexed breeches. We would agree with Ferguson *et al.* (1987) who reported a success rate of 65% for frank compared with 96% for flexed breeches. It has been suggested that the splinting effect of extended fetal legs interferes with successful version (Hofmeyr 1983).

The range of reported rates of spontaneous version has varied from 14–20% (Van Dorsten *et al.*, 1981; Brocks *et al.* 1984; Fall & Nilsson 1979) and includes the 17% reported in our series. Hofmeyr (1983), however, noted a high rate of 33% for spontaneous version and explained this partly by the tendency to late engagement of the presenting part in the African population. Our population in Zimbabwe is unlikely to be different from that in South Africa and therefore other factors may also have contributed to their high spontaneous version rate.

The impact of ECV on caesarean section rate is not well defined because of diverse strategies regarding the management of breech presentation at term. In our study, 33% and 13% in the control and ECV group, respectively, were delivered by caesarean section. Many other investigators have also demonstrated a reduction (Van Dorsten *et al.*, 1981; Hofmeyr 1983; Brocks 1984; Fall & Nilsson 1979). The side effects from the tocolytic agents were considered insignificant. Maternal complications for ECV must therefore be considered relative to those from caesarean section which carries a significant maternal mortality and morbidity.

The safety of ECV for the fetus is of vital importance. Very few complications occurred in this study. Fetal heart rate abnormalities were transient and may have resulted from a disturbance in oxygenation. Thus careful selection of patients suitable for ECV is important. As successful versions are usually accomplished within

5 min, we recommended stopping if version is not completed within 5 min. No fetal deaths have been reported after ECV at term without use of an anaesthetic. We were concerned by the one death associated with a tight cord around the neck. As this occurred 17 days after the ECV and the fetus remained active up to the time of delivery, we do not believe it likely that this death was related to ECV. Furthermore, 200 consecutive births in the unit revealed that two livebirths were also associated with a tight cord round the neck.

We conclude that ECV at term can substantially reduce the occurrence of breech presentation and also of caesarean section for breech presentation. The procedure is relatively easy, and all obstetricians should gain experience in ECV. If CTG facilities are lacking, presence of good fetal movements may be a reasonable assessment of fetal well-being before an attempt at ECV.

A clinically significant number of women are noted to have a breech presentation for the first time on admission to the hospital in labour. Ferguson *et al.* (1987) reported 15 attempts at ECV in such women with a success rate of 73%. Further research is needed to determine the role and timing of ECV in such women.

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Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years experience

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Summary. A total of 1628 women with CIN 3 treated with the Semm cold coagulator between 1975 and 1989 was followed primarily by cytology. The standard suitability criteria for ablation were adhered to except that patients were treated at their first visit when the colposcopist expected that the diagnosis would be no worse than CIN 3. Overall 97% of the women were treated at their first visit. In 30 women (2%) the histology was glandular or worse than expected, but 22 of these showed no persistent cervical disease subsequently. Follow-up was achieved for 87% at 10 years. In actuarial terms the primary success rate was 95% at 1 year and 92% at 5 years, it was similar for all age groups. Repeat cold-coagulation for persistent/recurrent CIN 3 was less successful and is not advised. The outcome for 226 pregnancies established after treatment is known. The rates for miscarriage, preterm or operative delivery were not increased. Cold-coagulation of CIN 3 at 100°C as performed by us is as effective as any other treatment and calls into question the need for more expensive practices.

Cervical intraepithelial neoplasia (CIN) is one of the most common gynaecological conditions encountered today. It is dealt with in a variety of ways either by excision or more frequently by destruction. A recent survey by the British Society for Colposcopy and Cervical Pathology (reported by H. Kitchener at their Annual Scientific Meeting in 1990) found that the cold coagulator was second only to the carbon dioxide laser as the most commonly used method. In marked contrast to laser treatment, very little has been published about cold coagulation which despite its name uses temperatures of up to 120°C.

The apparatus was initially introduced by Semm (1966) for the destruction of benign cervical conditions. Its applicability was tested in the cervix clinic of Ninewells Hospital and Medical School, Dundee in three patients in 1975 and since 1978 it has been the standard form of treatment for all CIN suitable for destruction. This is the longest running series in the United Kingdom and comes from an area where the incidence of invasive squamous cervical cancer continues to fall (Fig. 1).

Subjects and methods

Women are seen for colposcopy at the Ninewells Clinic if they have had two smears showing mild dyskaryosis or atypia or one smear showing moderate or severe dyskaryosis or cells suspi-

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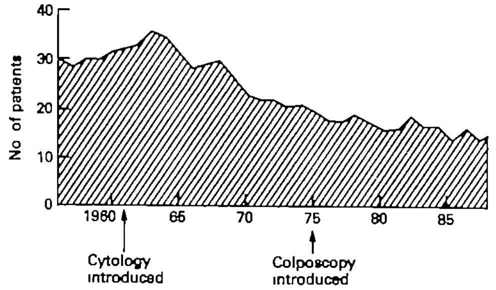

Fig. 1. Running 3-year averages of patients with invasive carcinoma of the cervix in the Dundee laboratories catchment area

cious of invasion. Colposcopy was performed using 3% acetic acid. If early invasion or glandular abnormality was suspected from the cytological or colposcopic appearances or if the squamocolumnar junction was hidden up the canal, then the transformation zone was excised. If colposcopically overt invasive carcinoma was seen, then treatment was given after confirmatory histology. In all other patients, two to four directed punch biopsies were taken. Immediately thereafter the transformation zone including the lower endocervix was destroyed at 100°C by overlapping 20-s applications of the thermoprobes. Usually between two and five applications were sufficient, taking less than 2 min and haemostasis was achieved by the very nature of the procedure. The woman was given a supply of triple sulphonamide cream for routine intravaginal use for the next week but normal sexual activity was not restricted. Follow-up was by cervical smears and colposcopy was only repeated if the original cytological criteria for referral were found again. The histological diagnosis was used to determine the frequency and duration of smear follow-up. Patients with a pre-treatment diagnosis of CIN 3 have smears repeated in the clinic at 4, 8, 12, 18 and 24 months. They are then seen by their general practitioners for annual smears for a further 8 years before reverting to the normal screening programme.

Details of the colposcopy, histology and initial follow-up were entered on a punch card and a microcomputer file kept separate from the patient's case notes. Details of follow-up smears were entered into the OCCURS computer (On-line Cervical Cytology Update and Recall System). This system currently serves Tayside, Fife and the Central Region of Scotland.

The punch cards were updated manually from the OCCURS computer before analysis. End points included persistent or recurrent histological abnormality (CIN 1 or worse), cone biopsy or hysterectomy (even when the histology was entirely benign) or death. Patients were deemed lost to follow-up when six months or more have elapsed since the last smear was due.

Patients

On 1st January, 1990, there were 1661 patients with CIN 3 treated consecutively with the cold-coagulator who were eligible for follow-up for periods of 4 months to 14 years. Thirty-three women have been lost without any follow-up data whatsoever and they have been excluded. The completeness of follow-up ranged from 98% at 4 months, through 87% at 5 years and 87% at 10 years. All the patients eligible for follow-up at 11 years and later have been seen (Table 1). Of the women lost to follow-up, 169 had normal smears, 94 (56%) of them had three or more normal smears consecutively, six others had had abnormal smears, three had a single mildly dyskaryotic smear and three had moderate dyskaryosis.

Thus 1628 women have been followed up. Their age distribution is shown in Figure 2; 1228 (75%) were <35 years of age, 23 (1·5%) were teenagers and 61 (3·5%) were ≥45 years. Figure 3 shows the parity distribution, 219 (13%) were nulliparous and 1024 (63%) had had not more than two pregnancies before treatment.

Results

Effectiveness

A single treatment was effective in restoring the cervical cytology to normal in 1518 of 1628 (93%) women followed-up. This is the primary success rate and was similar in the various age groups (Table 2).

Expressed in actuarial terms the primary success rate fell from 96% at 4 months, through 95% at 1 year, 94% at 18 months, 94% at 2 years, 93% at 3 years, 92% at 4 years, 92% at 5 years to 91% at 6 years and thereafter. Most 'recurrences' were probably persistent disease detected in the first 18 months of follow-up. Table 3 details the failures after a single treatment, they include one adenosquamous carcinoma, one squamous carcinoma, two invasive carcinomas (early stromal invasion) one moderate glandular atypia, 62 CIN 3, 19 CIN 2, 19 CIN 1 and abnormal cytology (as yet unresolved) in five women. One of these five women has severe

Table 1. Completeness of follow-up for 1628 patients with CIN 3 treated with cold-coagulation in Dundee

Follow-up (years)	Number	(%)
0·3	1628/1661	(98·0)
1	1362/1424	(95·6)
1·5	1196/1250	(95·7)
2	1061/1121	(94·6)
3	813/878	(92·6)
4	641/720	(89·0)
5	523/604	(86·6)
6	409/474	(86·3)
7	318/377	(84·4)
8	213/244	(87·3)
9	126/149	(84·6)
10	53/61	(86·9)
11	14/14	
12	2/2	
13	2/2	
14	1/1	

dyskaryosis, but has refused further investigation, four have moderate dyskaryosis (one declined further surgery and three have emigrated). Three women who were lost to follow-up after a single mildly diskaryotic smear have not been considered as failures.

The adequacy of cold-coagulation could be assessed histologically in hysterectomy or cone biopsy obtained subsequently from 99 patients; a lesion was suspected in 59 of them but was only confirmed in 42 (71·2%). Of 40 patients who had hysterectomies for unrelated conditions one had a focus of CIN 3, two of CIN 2, three of CIN 1, and 34 (85%) were clear.

Twenty-six patients with recurrent CIN 3 were treated on a second occasion with the cold coagulator (Table 4). This resulted in five failures (19%) comprising one adenosquamous carcinoma, one squamous carcinoma, one CIN 3 and adenocarcinoma *in situ* combined, one CIN 2 and one CIN 1. This adds credence to the belief that skip lesions can occur in a cervix that has been treated previously. We therefore consider that repeat treatment by this method is inadvisable and recommend excisional treatment if persistent or recurrent CIN 3 is suspected

Subsequent pregnancy

We know of 243 pregnancies among the treated women and the outcome in 226. Forty women (18%) had a legal abortion; nine (4%) had a first trimester miscarriage and three had ectopic pregnancies. The other 174 pregnancies resulted in deliveries. Three were preterm (two singletons at 35 weeks and one twin pregnancy at 27 weeks). The remainder went to term. Overall the caesarean section rate was 9% and the forceps rate 9%. Earlier in our series, we found that 94 of 101 women (94%) conceived within 2 years after treatment. Thus, the evidence is that cold-coagulation has no adverse effects on fertility or pregnancy outcome.

Inadvertent and possibly inappropriate treatment

Our policy of treating at the first assessment visit those women in whom colposcopically directed biopsies were expected to show CIN 3 at the worst differs from standard teaching. We are open to the criticism that we may treat glandular atypia, microinvasion and invasive carcinoma not suspected by the colposcopist both inadver-

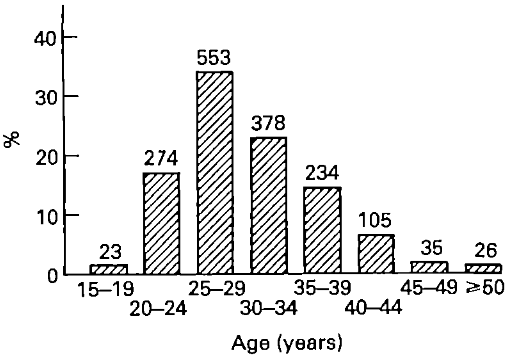

Fig. 2. Age distribution in 1628 patients with CIN 3 treated with cold-coagulation in Dundee.

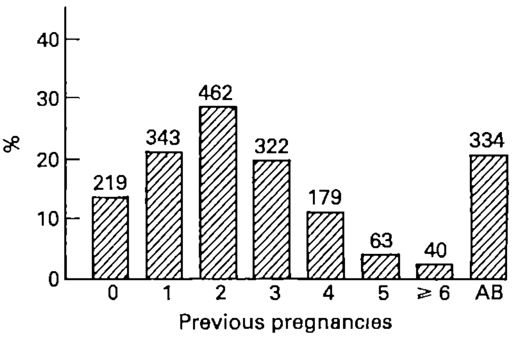

Fig. 3. Distribution by number of previous pregnancies in 1628 patients with CIN 3 treated with cold-coagulation in Dundee AB = abortions

Table 2. Simple failure rates for cold-coagulation therapy in 1628 patients with CIN 3 by age group

Age (years)	Number (%)
15–19	1/23 (4·3)
20–24	12/274 (4·4)
25–29	36/553 (6·5)
30–34	30/378 (7·9)
35–39	16/234 (6·8)
40–44	9/105 (8·6)
45–49	3/35 (8·6)
> 50	3/26 (11·5)
Total	110/1628 (6·8)

tently and inappropriately. Overall we treated 1584 of the 1628 women (97%) at their first visit and in 30 of them (2%) the lesion was more advanced than had been suspected (Table 5). The colposcopically directed punch biopsies revealed 14 squamous lesions including 12 microinvasive and two invasive carcinomas and 16 lesions with a glandular component, one of which was invasive. Further investigation showed that cold-coagulation, although inadvertent, had effectively destroyed the lesion in 22 of these 30 women. Residual disease was found in eight women whose management had not been compromised by their possibly inappropriate initial treatment. Unsupervised, inexperienced colposcopists should not treat patients at the first assessment visit, but we have demonstrated that the grounds for fearing that competent colposcopists should not do so are more imagined than real, provided that this is not done when the squamocolumnar junction is not visible, nor when glandular, microinvasive or invasive disease is suspected.

Table 3. Diagnoses in 110 failures of a single cold-coagulation treatment in 1628 patients with CIN 3

Diagnosis	Number
Severe dyskaryosis	1
Mod. dyskaryosis	4
CIN 1	19
CIN 2	19
CIN 3	62
GIN 2	1
Early stromal invasion	2
Squamous carcinoma	1
Adenosquamous carcinoma	1
Total	110/1628 (6·8%)

CIN = cervical intraepithelial neoplasia.
GIN = glandular intraepithelial neoplasia.

Discussion

The stability of the local population and the efficiency of the OCCURS system affords an excellent opportunity for longitudinal study. Even those patients deemed to have been 'lost', to follow up tend to reappear, e.g., 117 (70%) of 192 patients 'lost' on 1st January, 1987 were retraced by 1st January, 1990.

Relatively few women (4-5%) are service women or partners of servicemen or undergraduates who leave the area after temporary residence and are lost without trace, but this is unlikely to invalidate the findings from the vast majority who have been followed up.

Our overall primary success rate of 93% with a single treatment compares favourably with other reported centres using the same technique: 94-97% for 924 CIN 1-3 (Cassidy *et al.* 1987); 90% for CIN 2-3 (Smart *et al.* 1987); 97% for 71 CIN 2-3 (Staland 1978). Chanen & Rome (1983) have the longest running series of patients treated with electrocoagulation diathermy. Their primary success rate was 97% in 1864 patients with CIN (about 65% had CIN 3). Similarly 259 women with CIN 3 treated with cryosurgery had a primary success rate of 82%, this improved to 93% after a second treatment (Creasman *et al.* 1984).

Initially tissue destruction with the CO_2 laser was too superficial and good results depended on repeated treatments (Burke 1982). In a series of 40 patients with CIN 3, the primary success rate of 77·5% rose to 85% after a second treatment.

In a series of 419 patients with CIN 3 treated

Table 4. Diagnoses in five failures of secondary cold-coagulation treatment in 26 patients with recurrent CIN 3

Diagnosis	Number
CIN 1	1
CIN 2	1
CIN 3 + GIN 3	1
Sq. Ca	1
Adeno Sq. Ca.	1
Total	5/26 (19%)

CIN = cervical intraepithelial neoplasia
GIN = glandular intraepithelial neoplasia
Sq Ca. = squamous carcinoma.

Table 5. Details of 30 patients who received inadvertant possibly inappropriate cold-coagulation treatment

Squamous lesions	
Microinvasive (*n* = 12)	1 invasion to 5 mm on radical hysterectomy, nodes negative, a & w 1 CIN 3 on LLETZ 1 CIN 3 on cone 1 CIN 1 on cone 7 NAD on cone 1 NAD on smear follow-up
Invasive Sq Ca (*n* = 2)	2 invasion on radical hysterectomy, nodes negative, a & w
Glandular lesions	
GIN 3 (*n* = 5)	1 GIN 3 on LLETZ-GIN 1 on hysterectomy 1 NAD on hysterectomy 1 NAD on cone 2 NAD on smear follow-up
GIN 1/2 (*n* = 5)	5 NAD on smear follow-up
CIN 1/2+GIN 1 (*n* = 4)	4 NAD on smear follow-up
CIN 3+GIN (unspec) (*n* = 1)	12 persistent CIN 3
Invasive adeno Ca (*n* = 1)	1 NAD on radical hysterectomy, nodes negative, a & w

CIN = cervical intraepithelial neoplasia.
GIN = glandular intraepithelial neoplasia
Ca = carcinoma
NAD = no evidence of disease
a & w = alive and well.
LLETZ = large loop excision of the transformation zone.

by CO_2 laser vaporization, Anderson (1982) reported a primary success rate of only 74·4%, he suspected that the treatment had been too shallow. Later in the series the success rate improved to 81% with deeper treatment for various grades of CIN.

Subsequent series involving CO_2 laser vaporization to a depth up to 7 mm had more favourable results. Wright & Riopelle (1982) treated a series of 110 women with CIN 3 by CO_2 laser ablation and reported a primary success rate of 93% which improved to 99% after a second treatment. In a series of 129 patients with CIN 3, Jordan *et al.* (1985) reported a primary success rate of 88% in those treated to a depth of 5-7 mm. In a series of 1281 patients with CIN 3 treated over a period of 10 years, Baggish (1989) reported a primary success rate of 96%.

Cold-coagulation has been criticised on the basis of inadequate depth of destruction. Measurement of the depth of destruction is extremely difficult when the surface has been blistered off and the underlying tissue shrivelled by desiccation. Semm (1966) using the cold coagulator at 80-90°C for 15-25 s found that one application could achieve a destruction of 4 mm. De Cristofaro *et al.* (1988) showed that the depth of destruction ranged from 2·5 mm to 4 mm or more after treatment at 100°C for 30 s and always exceeded 4 mm after treatment at 120°C for 30 s. Haddad *et al.* (1988) found that the mean depth of tissue destruction ranged from 2·6 mm (100°C for 20 s) to 3·5 mm (120°C for 30 s).

If this were the case, then 4 mm depth of destruction would rarely be achieved in practice, yet this is the depth recommended by Anderson and Hartley (1980) based on their finding in 343 cone biopsies that the mean depth of involved crypts was 1·24 mm, thus destruction to a depth of 2·92 mm would eradicate all involved crypts in 95% and destruction to 3·80 mm in 97·7%. The difficulties in achieving accurate measurements of tissue destruction may account for any difference between the theoretical and the observed success of this instrument.

Clearly the cold-coagulator effectively destroyed CIN 3 in most of our patients but a few have progressed to microinvasive or invasive cancer. Microinvasion developed in two patients after a single treatment (one squamous and one adenosquamous cancer) and one squamous and one adenosquamous cancer occurred after repeated treatment. The cervical screening programme is aimed at preventing squamous rather than adenocarcinoma. Again the cold-coagulator is comparable with other treatment methods in this respect Pearson *et al.* (1989) reported the development of invasive cancer in four of 2193 patients with CIN 3 treated by laser ablation (three squamous carcinoma and one adenocarcinoma) and four others developed microinvasion. Townsend *et al.* (1981) reported a survey of the Society of Gynecologic Oncologists which identified 20 patients who had developed invasive cancer after cryosurgery or hot cautery after colposcopically directed biopsy. Cone biopsy and even hysterectomy for CIN 3 do not always prevent the subsequent development of invasive cancer. Webb (1985) reported the development of invasion in 34 of 5616 (0·6%) women from collected series of patients treated by cone biopsy compared with 19 of 5200 (0·4%) women treated by hysterectomy.

Primary success rates are fundamentally important. Our failure to eradicate disease in 5 of 26 patients treated on a second occasion highlights not so much a failing of the technique, but rather an important difference between an untreated and a previously-treated cervix. In the former, skip lesions are assumed to occur rarely if ever but may well be present in the latter. We would advise excision of the transformation zone in a patient with persistent or recurrent CIN 3 rather than repeat destruction.

The value of any treatment is measured not only by its success but also by its acceptability which depends on various factors including side effects and complications. We did not assess these formally but patients volunteered very few. In women treated for cervical erosions (Ferguson & Craft 1974), pain was experienced by 5 of 24 treated by cold-coagulation, but by none of 27 treated by cryosurgery, a watery discharge was experienced by only four of the former compared with 25 of the latter. Farquharson *et al.* (1987) randomized 714 patients with CIN 2 or 3 to treatment by cold-coagulation or laser vaporization and found that cold-coagulation was significantly shorter, less painful, and less likely to produce secondary haemorrhage.

The most important determinant of unimpaired cervical function is fertility and pregnancy outcome. Duncan (1983) reported a conception rate of 94% within 2 years of treatment. We now have records of 226 pregnancies in women who were treated by cold-coagulation for CIN 3 and their outcome was as good as in untreated women.

Most women with an abnormal smear experience anxiety which is at its peak when awaiting colposcopy and only marginally less so when awaiting treatment (Posner & Vessey 1989). These women benefit greatly from treatment at the first visit. We believe that competent examiners can distinguish almost always between microinvasive or invasive cancer where destruction is inappropriate, and the cervix containing CIN or viral changes. Our experience, in a clinic where 20 operators have been trained by one consultant during 14 years, would support this assertion. All patients (including CIN 1 and 2 and less severe lesions) are treated with a simple uncomplicated technique which does not compromise the cervix in any recognizable way. Only 44 (3%) of our 1628 patients had to endure an anxious wait for histology which then proved to be normal. This seems to us to be a very large plus to set against the 0·5% of women with CIN 3 whose initial treatment was perhaps inappropriate. Considering we treated a large number of women with lesions less severe than CIN 3, inappropriate treatment was only given to a fraction of 0·5% and in none of them was the definitive treatment compromised.

Costing much the same as a small cryosurgical unit, the Semm coagulator runs conveniently and inexpensively on mains electricity. Small and light, it is readily portable. Its operation is silent and the treatment temperature of 100°C is insufficient to produce charring. The consequent absence of smoke and smell avoids the additional cost of smoke extraction and contributes to a high acceptability by patient and doctor alike. Because of the extremely short duration of the treatment, most women find the associated discomfort tolerable; 1550 of 1628 women (95%) has no anaesthesia whatsoever. The variety of thermoprobes allows uniform treatment of lesions regardless of size or shape provided they meet the generally accepted criteria for local destruction. Post-operative discharge and bleeding are not a problem for most patients. Fertility and the outcome of subsequent pregnancy are not adversely affected.

Our carefully audited experience over many years has convinced us that cold-coagulation is the most cost effective method for the destruction of CIN 3. Our results are as good as those published for any method of treating CIN 3. We treat most women at their first visit and reserve follow-up colposcopy for those with abnormal smears. Salfield & Sharp (1989) attempted to quantify colposcopic requirements assuming that treatment is not given at the first colposcopic assessment and that colposcopy is used routinely on the follow-up of treated patients. Lopes *et al.* (1990) questioned the value of routine colposcopy follow-up. Our study calls into question not only the excessive demands that colposcopy is making upon current resources, but also the need for more expensive forms of treatment.

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A randomized control trial of two cervical spatulas

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Summary. The sampling efficacy of the Ayre and Rocket cervical spatulas was compared in a randomized controlled trial involving 533 women who were attending a colposcopy clinic either for investigation of cytological abnormality or for review after treatment of CIN. Smears were compared with respect to the presence of cytological abnormality and two types of normal cervical epithelial cells (endocervical and immature metaplastic cells) which are considered indicators of adequate cytological sampling. Smears taken with the Rocket spatula were significantly less likely to contain immature metaplastic cells (95% CI on difference in proportion; 5–30%), but more likely to contain endocervical cells (95% CI 16–36%). No significant difference was found in the proportion of smears containing one or other type of indicator cell or in the yield of abnormal smears. It is concluded that the Rocket spatula offered no advantage when used in these circumstances. This study illustrates how spurious conclusions of sampling efficacy can be drawn if only one type of indicator cell is used as an endpoint.

Efforts to produce a spatula which yields a greater proportion of adequate smears are always to be encouraged. However, preoccupation with the sampling instrument may divert attention away from other explanations for inadequate sampling, for example, the competence of the smear taker. Furthermore, new spatulas invariably cost more than their predecessors, the Aylesbury spatula which has been recommended by the DHSS (1988) costs between 3 and 4 times as much as the Ayre spatula (Mersey Regional Health Authority). The introduction of new designs of spatulas can therefore have substantial resource implications and require careful evaluation. The object of this trial was to compare the efficacy of the Ayre and Rocket spatulas (Figure 1) using different indicators of adequate cytological sampling.

Subjects and methods

The study population comprised women attending the colposcopy clinics at the Birmingham and Midland Hospital for Women for investigation of cytological abnormality or for review following treatment of cervical intraepithelial neoplasia (CIN). All smears were taken following colposcopic inspection of the cervix and before the application of acetic acid. The presence of endocervical cells, immature metaplastic

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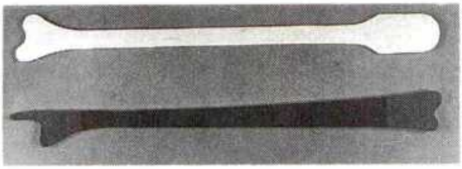

Fig. 1. Cervical spatulas used in the study. The Rocket spatula is made of dark plastic and is shown below the Ayre spatula which is made of wood.

cells and cytological abnormality was recorded by laboratory personnel who were unaware of which spatula had been used to take the sample. The validity of using endocervical and immature metaplastic cells, which are normal cervical epithelial cells with well defined cytomorphology, as indicators of adequate cytological sampling has been reported elsewhere (Woodman *et al.* 1989; Patten 1978). A smear was considered abnormal if it contained cells with atypical enlarged nuclei, dyskaryotic cells, malignant appearing squamous cells consistent with a CIN 3 lesion or features suggestive of invasive change.

The unit of randomization was a week of colposcopy sessions and not as is usual the individual patient. This unit was primarily chosen to facilitate the compliance of the four participating clinicians. At the beginning of each week one type of spatula was allocated to all colposcopy sessions occurring in that week and spatulas of the other type withdrawn from the clinic area. Clinicians were thus obliged to use each spatula for a period of 15 weeks.

Statistical analysis

As a form of group or cluster randomization was used to allocate the women it is necessary to consider the possibility of intra cluster dependency when estimating an appropriate standard error for the difference between proportions for each response variable. This need arises because the independence of observations made on individuals within cluster cannot be assumed. For example, the usual practice in our laboratory is for a technician to examine all the smears taken from a particular colposcopy clinic. This may result in a tendency toward homogeneity when recording the presence or absence of certain response variables in smears taken from this cluster of subjects.

Calculation of the appropriate standard errors, therefore, requires computation of a clustering parameter. This measures the extent to which agreement in a cluster exceeds that expected by chance; when the clustering parameter is 0, all observations made on the group can be considered independent; when it is 1 a cluster behaves as a single individual, as all observations have an equal probability of being either positive or negative (Donner *et al.* 1981). When substantial intra cluster dependency exists the result is a shrinkage of effective sample size and consequently an increase in the variance estimate.

We have estimated a clustering parameter for each response variable and used this to compute correction factors for each cluster size (Donald & Donner 1987). 95% confidence intervals, based on these estimates, have been constructed around the differences in proportions between the two spatulas for each outcome measure.

Results

The two spatula groups were comparable in their age and treatment status (Table 1). Clustering parameters of 0·02, 0·09, 0·02, and 0·03 were estimated for endocervical, imature metaplastic, endocervical or immature metaplastic and abnormal epithelial cells respectively. Smears taken with the rocket spatula were significantly less likely to contain immature metaplastic cells but more likely to contain endocervical cells; no significant difference was found in the yield of abnormal smears or the proportion containing one or other type of indicator cell (Table 2). No advantage was found with use of the Rocket spatula in any of the treatment groups; smears taken after cone biopsy were less likely to contain indicator cells irrespective of which spatula was used (Table 3).

Discussion

The principal methodological problems encoun-

Table 1. Comparability of the two spatula groups

	Ayre	Rocket
Variable	(n = 248)	(n = 285)
Mean age (SD)	31·8 (9·5)	31·6 (8·4)
Pretreatment	130 (52%)	153 (54%)
Post-laser vaporization	79 (32%)	85 (30%)
Post-cone biopsy	39 (16%)	47 (16%)

Table 2. Relation between spatula type and presence of indicator cells

Indicator	Number (%) of smears containing indicator cells: Ayre (*n* = 248)	Rocket (*n* = 285)	95% CI on difference in proportions (%)
Endocervical cells	59 (24)	142 (50)	(16 to 36)
Immature metaplastic cells	168 (68)	143 (50)	(4 to 30)
Endocervical or immature metaplastic cells	186 (75)	218 (76)	(−7 to 10)
Abnormal epithelial cells	101 (41)	129 (45)	(−6 to 15)

tered in the comparison of different spatulas relate to the selection of end points and control of confounding factors. One or more of the following endpoints have been used to compare smears taken with different spatulas in different studies: number of epithelial abnormalities detected, presence of endocervical cells alone, presence of endocervical and/or metaplastic cells, number of squamous cells seen and cellular quality (Bounds *et al.* 1976; Bourne & Beilby 1976; Wolfendale *et al.* 1987; Pistofides *et al.* 1984). The most directly relevant measure of sampling efficacy is the detection rate of cytological abnormality. The problem with using this endpoint is the large sample size required. Only the Aylesbury spatula has been shown to yield a significantly higher rate of detection of cytological abnormality. Wolfendale *et al.* (1987) compared the Aylesbury and Ayre spatulas in a randomized trial involving 1700 smears. Overall, 3·5% of smears taken with the Aylesbury spatula contained dyskaryotic cells compared with 2·9% of those taken with the Ayre spatula. However, the importance of this observation is uncertain because: (i) the statistical analysis was based on individual responses although a form of group randomization similar to that used in the present study was used, and (ii) the significant difference between the two spatulas was confined to the detection of dyskaryotic smears and disappeared when all grades of cytological abnormality are included in the analysis To overcome the problem of sample size, we used a population known to have a high prevalence of cytological abnormality—women attending a colposcopy clinic for investigation, treatment and follow up of cytological abnormality.

If this trial had used endocervical cells as the sole endpoint, it might have been concluded that the Rocket spatula was a superior sampling instrument. In fact, there was no difference between the two spatula types with respect to either the detection rate of cytological abnormality or the number of smears containing at least one type of indicator cell. A more striking example of the different conclusions that can be drawn when different endpoints are used was provided by a study comparing the Ayre and Armovical spatulas (Bourne & Beilby 1976). That study used a paired spatula design, i.e., two smears were taken from each of 10 690 women. For the first half of the study smears were taken first with the Ayre spatula, for the second half the order was reversed. The authors draw conclusions based on all study smears although they acknowledge that previous workers had demonstrated a discrepancy of atypical elements when two simultaneous smears are collected. However, they do present the information necessary to make a more valid comparison—one confined to the first of each pair of smears. When the data are reanalysed in this way, a surprising discordance between the two outcome measures emerges. Smears taken with the Armovical spatula were significantly more likely to contain endocervical cells, but the detection rate of epithelial abnormality was significantly better with the Ayre spatula.

Table 3. Relation between treatment, spatula type and adequacy of sampling

Treatment	Smears containing endocervical or immature metaplastic cells: Ayre *n* (%)	Rocket *n* (%)
Pretreatment	108 (83) (*n* = 130)	131 (86) (*n* = 153)
Post-laser	59 (75) (*n* = 79)	65 (76) (*n* = 85)
Post-cone	19 (49) (*n* = 39)	22 (47) (*n* = 47)

The Rocket spatula shares a common design modification with a number of other spatulas—an elongated tip to facilitate access to the endocervical canal (Bounds *et al* 1976; Wolfendale *et al.* 1987; Pistofides *et al.* 1984). They are all therefore more likely to pick up endocervical cells, but not necessarily more likely to provide an adequate smear. To illustrate this point by a *reductio ad absurdum* consider a pin as a sampling instrument. If introduced into the cervix, it will easily pass through to the endocervical canal and almost inevitably there will be some endocervical cells on its tip, but it can hardly be said to have taken an adequate smear. If a spatula is specifically designed to pick up endocervical cells it may well do so. The danger is that the presence of endocervical cells on a smear will cease to indicate that the transformation zone has been sampled and merely reflect the design modification. Opinions based on spatula trials using the presence of endocervical cells as the sole outcome measure should be disregarded.

The smear takers in this study were not typical of those engaged in population screening. All were experienced gynaecologists, all had the advantage of taking a smear under optimum conditions This lessened the possibility of bias arising from the competence of different smear takers (Vooijs *et al.* 1986) but reduces the extent to which the findings can be generalised. It is conceivable, albeit unlikely, that a substantial advantage might still follow the use of the Rocket spatula in the general screening situation.

This study did not collect information on other factors claimed to affect the adequacy of cytological sampling and these are now considered. Bounds *et al.* (1976) found no effect attributable to stage of the menstrual cycle. Vooijs *et al.* (1987) showed that smears taken during the first 4 days of the cycle were likely to be inadequate but that the variation observed during the remainder of the cycle was too small to be of practical importance (Vooijs *et al.* 1986). Both these investigators found that the proportion of smears not containing endocervical cells was significantly higher among women using hormonal methods of contraception but the magnitude of the difference was only 8% (Vooijs *et al.* 1987) It is unlikely that either of these factors could have substantially influenced the results of this study

The strategy of comparing the two spatulas in a population with a high prevalence of cytological abnormality appears sound. It is difficult to imagine how women referred to a colposcopy clinic for assessment of cytological abnormality differ substantially from those with as yet undetected cytological abnormality in the unscreened population. This approach is recommended for future spatula trials.

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Vaginal epithelial abnormalities in patients with CIN: clinical and pathological features and management

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Summary. Of 4147 women who had CIN treated by laser at the Regional Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, 103 (2·5%) had co-existing vaginal epithelial abnormalities. CIN 3 was the histological diagnosis most often associated with vaginal lesions. The upper vagina was almost always involved. In 67% the lesion in the cervix appeared to be confluent with that in the vagina. Even when the lesions were confluent, biopsies form the cervical and vaginal components did not always show the same grade of intraepithelial neoplasia and in some biopsies they showed different lesions. Laser treatment appears to be effective for the vaginal lesions and is therefore recommended although, in selected patients, careful follow up alone may suffice.

There is some controversy as to how much of the vagina is derived from the paramesonephric ducts (uterovaginal canal) and how much from the urogenital sinus. One of the more popular theories is that the uterovaginal canal and cells derived from its lower end give rise to the epithelial lining of the uterus and to at least part of the vagina but it has also been postulated that the whole of the vaginal epithelium is derived from the endoderm of the urogenital sinus (Hamilton *et al.* 1978). Colposcopic evidence of the existence of both columnar and stratified squamous epithelia on the ectocervix and in the vaginal fornices at the same of different times, the changing boundary between these two epithelial types in these areas and their ability to undergo metaplasia, strongly supports the hypothesis that they are derived from the same embryologic structures. Similarly, the response of the epithelia of the ectocervix, vagina, perineum and peri-anal region to viral infections and other environmental influences, and the abnormal changes that occur in these areas—from atypia to frank invasive cancer—also tend to suggest common origins. This paper examines the clinical and pathological features of vaginal lesions in relation to the co-existing cervical lesions and describes their management.

Patients and methods

The case records of the 4743 patients treated by laser for cervical epithelial abnormalities at the Regional Gynaecological Oncology Centre at the Queen Elizabeth Hospital, Gateshead between January 1978 and March 1989 were reviewed. The records of 4147 of these patients provided sufficient data for inclusion in the analysis. In 103 of them (2·5%) vaginal epithelial abnormalities co-existed with lesions in the cervix. Forty of the vaginal lesions had been biopsied and examined histologically

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Results

The time of diagnosis of the vaginal lesions was examined in relation to the time of diagnosis of the co-existing cervical lesions. Although 68 (66%) of the 103 vaginal lesions were identified at the first colposcopic examination, at which the cervical lesion was diagnosed, they were missed in 34 (33%). Sixteen patients (15·5%) had their vaginal lesion diagnosed at a second or subsequent colposcopic examination, before treatment of the cervical lesion. The vaginal abnormality was discovered only after treatment of the cervix had failed to clear abnormal cytology in 19 patients (18·5%); 17 of them had persistent or recurrent abnormal cytology within 12 months of treatment of the cervical lesion and two had recurrent abnormal cytology more than 18 months after apparently successful treatment of the cervical lesion.

The fornices and upper third of the vagina were involved in 99 of the patients (with no involvement of the other areas in 92). The middle and lower thirds were involved in nine and three patients respectively; eight of these 12 patients had a vaginal biopsy and seven showed wart virus infection only , and in the other one the histology was equivocal.

The abnormal vaginal epithelium was described by the usual combinations of colposcopic terms (Table 1). As expected, no colposcopic appearance or description could be said to be specific for any particular histological diagnosis in the 40 vaginal lesions that were biopsied (Table 2). In 69 out of the 103 patients (67%), there was anatomical continuity between some or all of the lesions in the cervix and those in the vagina. Lesions in the vagina were deemed not to be extensions of those in the cervix if there was a bridge of healthy epithelium between them. Of the 40 vaginal biopsies 25 had lesions that were continuous with those in the cervix. The histology of the vaginal biopsy was not always the same as that of the cervical biopsy, whether or not the lesions were in anatomic continuity (Table 3) but VAIN 3 only occurred in the presence of CIN 3 (Table 2).

By 1978 the carbon-dioxide laser had replaced all other forms of treatment for CIN at the Regional Gynaecological Oncology Centre and all but one of the cases reviewed had received laser treatment. The cervix was usually treated to a depth of 7–10 mm and the vagina to a depth of 3–5 mm. Treatment was considered successful only if colposcopy and smears remained negative for at least 18 months following treatment. The exception to laser treatment was a 52-year-old patient in whom partial vaginectomy was combined with total abdominal hysterectomy and bilateral salpingo-oophorectomy, as she also had dysfunctional uterine bleeding. In two patients the vaginal lesions had disappeared spontaneously before treatment could be given. They were both pregnant when they attended for treatment, which was therefore deferred, but when they returned 3 months after delivery the vaginal lesions had regressed spontaneously and only the cervix was treated. One of these patients had biopsies of the cervix and vagina: both biopsies showed wart virus infection. In the other patient, whose vaginal lesion was not biopsied, the cervical lesion was CIN 3.

Discussion

It is usually assumed that abnormal squamous cells in a smear have come form the ectocervix but adnormality involving multiple areas of the lower genital tract simultaneously is not rare. Many colposcopists do not routinely examine the vagina as carefully as the cervix, which involves risk of failing to detect vaginal epithelial abnormalities. Fortunately, where cervical and vaginal epithelial lesions co-exist they are usually in anatomical continuity (in 66% in our study) so that the lesion in the cervix, which is easily identified, attracts attention to the lesion in the vagina. If the lesions are not close together, discovery of the vaginal abnormality may be delayed until a more thorough search of the lower genital tract is made, sometimes after treatment of CIN has failed to render the cytology normal. One patient had a cone biopsy on the assumption that the lesion must be out of sight in the cervical canal but histology did not show any abnormality. Careful colposcopic examination, including the vagina, must be undertaken before embarking on a cone biopsy whenever an abnormal smear persists after treatment of a cervical lesion.

The distribution of epithelial pathology in the fornices and upper third of the vagina in 99 (96%) of our 103 patients is consistent with the reported involvement of the vault in 97% of a series of 101 post-hysterectomy patients with abnormal smears (Benedet *et al.* 1977) and involvement of the upper third of the vagina in 88% of a series of 59 patients with VAIN (Lenehan *et al.* 1986). These observations support the

Table 1. Colposcopic description of abnormal vaginal epithelium

Description	Number of patients
ACWE*	31
ACWE + mosaic	15
ACWE + punctation + mosaic	25
Condyloma, wart, warty, 'wet skin' look	17
Condyloma + ACWE + punctation + mosaic	1
'Leukoplakia'	2
Area only iodine negative	2
Not described	10
Total	103

*ACWE = Aceto-white epithelium

concept of a common embryologic origin and shared risk factors for the epithelia of the ectocervix and upper vagina.

The grade 3 lesion was the most common histologic diagnosis in our patients. We cannot explain the higher proportion of wart virus infections in the vagina (27.5% in this series and 29% in the series by Lenehan *et al.* 1986) compared with the cervix (18.4%). Predictions of histological grade of cervical pathology based on colposcopic appearances are quite often erroneous. The errors are more flagrant in respect of the vagina because the colposcopic appearances and staining reaction with acetic acid and Schiller's iodine can vary considerably for any given degree of histological abnormality. In one patient (no. 30, Table 2) an area harbouring VAIN 3 did not stain abnormally with acetic acid but was identified by application of iodine. Conversely however, abnormal staining with iodine may represent minimal or no epithelial abnormality and can be due simply to immaturity of the cells (Crompton, 1976). Some of the vaginal biopsies that showed histological evidence only of wart virus infection (nos. 2, 15, 32, 40, Table 2) were from areas staining acetowhite, with or without punctation or mosaic, suggestive of VAIN 3.

Confluent vaginal and cervical lesions may be dissimilar histologically because of different rates of progression or regression in different areas of the confluent lesion. Alternatively, the apparent differences may merely reflect sampling from areas of mixed severity. Inconsistencies in the interpretation of biopsy material, not uncommon in intraepithelial neoplasia, may also explain some of the differences.

Bridges of healthy epithelium, produced by partial regression of previously confluent lesions, may separate lesions in the vagina, particularly those in the fornix, from those on the cervix. The histology of such separated lesions may then be similar (nos. 1, 7, 24, 25, 26, 30, 37 and 40, Table 2). Vaginal lesions separate from those on the cervix may also develop in accordance with the multicentric field change theory (Newman *et al.* 1959; Marcus *et al.* 1960) and may or may not then be histologically similar to the cervical lesion.

These considerations have relevance to the treatment options. Hysterectomy with a cuff of vagina does not completely eliminate the risk of residual or recurrent lesions (Benedet *et al.* 1977) Frequencies of between 0·9 and 6·8% have been reported for VAIN after such operations for CIN (Gallup & Morley 1975; Woodruff 1965). In Tayside, recurrence was confirmed in only two (1%) of 219 cases treated by hysterectomy, in a 15-year follow-up study (Gemmell *et al.* 1990). Since these women require continuing surveillance, hysterectomy would seem too drastic an option unless there is also some other uterine pathology. Although local irradiation can destroy VAIN (Woodman *et al.* 1988) this benefit must be weighed against possible longer term disadvantages, including distortion and narrowing of the vagina, a potential for inducing neo-epithelial abnormalities and making subsequent interpretation of vaginal cytology very difficult. Topical agents such as 5-fluorouracil give unreliable and unpredictable results (Ireland & Monaghan 1988)

Our results suggest that the carbon dioxide laser is effective in treating vaginal epithelial abnormalities. It can deal with multiple sites and because scarring is minimal there is little or no loss of function. There is no interference with cytological follow-up. Residual and new lesions can be treated without mutilating the patient. The usual precautions of exclusion of invasive disease, accessibility of all the lesion and correct assessment of depth of treatment must be observed.

Vaginectomy combined with construction of a neo-vagina may be the only option when other forms of treatment fail or if the lesions are not accessible to ablative therapy, such as in the vaginal angles after hysterectomy. This is a daunting surgical procedure and even when it has been successful, follow up must continue. Intraepithelial neoplasia has developed in an

Table 2. Anatomical and pathological relation between cervical and vaginal lesions

Serial no.	Histology of cervical lesion	Site of vaginal lesion(s) and relation to cervical lesions	Vaginal lesions	
			Colposcopic description	Histology
1	CIN3	Patchy, affecting the left fornix; not continuous	ACWE with punctation	VAIN 2-3
2	WV1	Posterior fornix and post vag. wall to halfway down the vag. lesion in fornix, continuous	ACWE with mosaic	WV1
3	CIN3 + WV1	Anterior fornix, cont with lesion on ant lip of cervix	ACWE with mosaic	VAIN 3 + WV1
4	CIN3	Discrete patches on ant fornix Lesion in post fornix cont. with lesion on post lip of cervix	ACWE	VAIN 3
5	CIN3	Ant and post fornices, cont. with lesions on lips of cervix	ACWE, punctation mosaic	VAIN 3
6	CIN3	Post fornix; cont with lesions on post. lip of cervix	Dense ACWE punctation mosaic	VAIN 3
7	WV1	Left fornix and upper vagina; not continuous	'condylomatous'	WV1
8	CIN2	Ant fornix, continuous	ACWE	VAIN 2
9	CIN2	Post. fornix, continuous	ACWE	VAIN 2
10	CIN3	Post and right lateral fornices, not continuous	Not described	VAIN 3 + WV1
11	CIN3	Ant fornix, continuous	ACWE punctation	VAIN 3
12	CIN3	Ant fornix; continuous	ACWE, marked punctation & vascularity	VAIN 3
13	CIN3	Ant fornix, continuous	Not described	VAIN 3
14	CIN3	Ant fornix, continuous	Not described	VAIN 3
15	WV1	Right fornix, continuous	ACWE, coarse mosaic	WV1
16	CIN3	Ant & post. fornices, cont Also discrete patch on ant. vaginal wall	ACWE	VAIN 3
17	CIN2	Ant & Post fornices, continuous	Not described	VAIN 2
18	CIN2	Ant fornix, continuous	ACWE, punctation mosaic	VAIN 2
19	CIN3	Ant. fornix; continuous	ACWE	VAIN 3
20	CIN3	Fornices, continuous	ACWE punctation mosaic	VAIN 2-3
21	CIN3	Ant & post fornices, continuous	Faint ACWE	N A D
22	WV1	Fornices; not continuous	ACWE, 'satellite' lesions	WV1
23	CIN2	Post. fornix, not continuous	ACWE	WV1
24	WV1	Ant & lat fornices, not continuous	'Warty lesions'	WV1
25	CIN3	Post fornix, not continuous	ACWE, punctation mosaic	VAIN 3
26	CIN3 + WV1	Right fornix, not continuous	'Condyloma'	VAIN 3 + WV1
27	WV1	Vaginal fornices; not continuous	ACWE? warts	N A.D
28	CIN2	All fornices, upper third of vagina; continuous	ACWE	WV1
29	CIN3	Ant & post fornices; continuous	ACWE, mosaic	N A D
30	CIN3	Right & left fornices, not continuous	Iodine—ve areas	VAIN 2-3
31	N A D	Multiple lesions in fornices; not continuous	'Warts'	N A D.
32	CIN1 + WV1	Ant & post fornices; continuous	ACWE, punctation	WV1
33	CIN3	Ant & post fornices; continuous	ACWE, mosaic	VAIN 3
34	CIN2 + WV1	Left fornix; continuous	ACWE, mosaic punctation	*VAIN + WV1
35	CIN3	Post fornix; continuous	ACWE	VAIN 3
36	WV1	All vagina, not continuous	'Warts'	WV1
37	WV1	Right fornix, not continuous	'Warts'	WV1
38	CIN3 + WV1	Left postero-lateral fornix; continuous	ACWE	VAIN 3 + WV1
39	CIN3	Ant & post. fornices, not continuous	ACWE mosaic	VAIN 3
40	WV1	All over upper vagina, not continuous	ACWE punctation	WV1

*Grade of VAIN not stated

ACWE = aceto-white epithelium, VAIN = vaginal intraepithelial neoplasia, WV1 = wart virus, CIN = cervical intraepithelial neoplasia

Table 3. Summary of relation between vaginal and cervical lesions in 40 biopsies

	Histology		
Vaginal lesions	Similar to histology of cervix	Dissimilar	Total
Continuous with cervical lesions	22	4	26 (65%)
Discrete from cervical lesions	10	4	14 (35%)
Total	32	8	40

artificial vagina (Imrie *et al.* 1986) and frank carcinoma has been reported following all forms of treatment for intraepithelial neoplasia short of total vaginectomy (Benedet *et al.* 1984; Lenehan *et al.* 1986; Gallup *et al.* 1975).

Withholding all forms of treatment of vaginal lesions and following up the patients at regular intervals with cytology and colposcopy may be an acceptable alternative form of management provided there is no clinical, colposcopic, cytological or histological evidence of progression. This approach takes account of the uncertain nature and behaviour of vaginal epithelial lesions and their tendency to regress during long term follow-up (Gemmell *et al.* 1990).

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Treatment of anovulation due to polycystic ovarian syndrome by laparoscopic ovarian electrocautery

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Summary. Our experience of ovarian electrocautery for the treatment of polycystic ovarian syndrome (PCOS) in ten women is described. We found that nine responded favourably, either ovulating spontaneously or becoming more responsive to ovulation induction. There was a significant and persistent fall in serum testosterone levels, and a transient fall with subsequent rise in inhibin. We recommend that laparoscopic ovarian electrocautery is considered as an alternative to ovulation induction with gonadotrophins, in women with PCOS who fail to respond to clomiphene citrate.

It is now more than half a century since Stein & Leventhal (1935) first described the clinical syndrome of amenorrhoea and bilateral polycystic ovaries, often associated with hirsutism, but our understanding of the patho-physiology of this condition has improved only a little. With the development of assays for gonadotrophins, it became apparent that women with polycystic ovarian syndrome (PCOS) had inappropriately elevated levels of serum luteinizing hormone (LH) (Baird *et al.* 1977), which was believed to interfere with folliculogenesis.

Stein & Leventhal (1935) advocated wedge resection of the ovaries as a therapeutic measure and reported seven women in whom the surgery restored physiological function completely, with return of regular menstruation in all, and pregnancy in two. This mode of treatment became widely accepted, as it was the only treatment available before the 1960s.

Stein (1965) reported a series of 108 women who had had bilateral wedge resection of the ovaries resulting in menstruation becoming cyclic in 95% and pregnancy in 71 of 83 (85%) women who wished to conceive. He also reported that the effect was permanent and that post operatively, the women menstruated regularly and remained fertile throughout their normal reproductive years, with no recurrence of PCOS in his entire series.

Another large retrospective study of wedge resection by Adashi *et al.* (1981) reported the resumption of menstrual cyclicity in 95% of women treated, with a crude overall conception rate of 47·8%, and a predicted cumulative conception rate after 10 years, as determined by life table analysis, of 73%. They drew attention to the significant occurrence of tuboperitoneal disease in their series, and although their minimum frequency of tubo pelvic disease was 7·8%, they pointed out that only a small proportion of

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women had been investigated again and therefore this was an under-estimate. It therefore became apparent that ovarian wedge resection not only required major surgery but was also associated with complications such as pelvic adhesions on follow-up. Toaff *et al.* (1976) reviewed seven women who had ovarian wedge resection and made a '. . . plea to relegate the surgical approach to a minor position in patients with Stein-Leventhal syndrome . . .'

Alternative treatment of anovulation in women with PCOS became available with the release of clomiphene citrate and this is now accepted as the treatment of first choice (Franks *et al.* 1985). Rates of ovulation between 67 and 76% have been reported; but pregnancy rates are less in women with PCOS. The next option is ovulation induction using human gonadotrophins either of menopausal or pituitary origin. A recent review of the Australian experience with human pituitary gonadotrophin (hPG) showed that of 1544 women treated, 148 had elevated LH levels and presumably PCOS and these women had significantly lower ovulation and pregnancy rates than women with normal LH levels (Kovacs *et al* 1989*a*).

Further advances in ovulation induction for women with PCOS have been the introduction of purified follicle-stimulating hormone (FSH) (Seibel *et al.* 1985), and human menopausal gonadotrophin (hMG) in combination with an LHRH agonist (Buckler *et al.* 1989). Whether either of these developments will improve pregnancy rates remains to be determined.

Pulsatile subcutaneous infusion of GnRH has revolutionized the approach to clomiphene citrate resistant anovulation, but in our experience (Kovacs *et al* 1989*b*) the outcome in women with PCOS was most disappointing. Other workers have reported better results with ovulatory rates of up to 61% (Chen *et al.* 1988).

The surgical approach is as successful as these medical treatments, but was largely abandoned because of the need for laparotomy and subsequent pelvic scarring. Wedge resection of the ovaries also had the advantage of providing a permanent cure, whereas medical treatment only induced ovulation and maybe achieved pregnancy without restoring regular menstruation. Therefore, when ovarian electrocautery under laparoscopic vision was described (Gjonnaess 1984), with a post operative ovulation rate of 92% in 62 women treated, there was renewed interest in the surgical approach Confirmatory evidence came from Greenblatt & Casper (1987) who reported ovulation in 5 of 6 women treated by ovarian electrocautery. Preliminary hormonal studies after ovarian cautery were reported by Greenblatt & Casper (1987) in six women; they reported a decrease in androstenedione, testosterone, oestradiol and LH levels after surgery.

Gjonnaess & Norman (1987) studied hormone levels in 16 women before surgery, the morning after and 5–6 weeks later. They found that LH increased post operatively and was associated with an enhanced response to GnRH of both LH and FSH.

In the present study we set out to assess the value of ovarian cautery in a group of women in whom medical treatment had not succeeded, and to further study the hormonal changes resulting from surgery. In addition we have measured inhibin levels.

Patients and methods

The ten women selected for the study all had long standing anovulation secondary to PCOS. The diagnostic criteria of the PCOS included oligomenorrhoea or secondary amenorrhoea, an inappropriately elevated LH and normal, or low FSH in the presence of follicular phase levels of progesterone. All the women had failed to ovulate despite taking clomiphene citrate in a dose of 150 mg daily for 5 days. Seven had previous cycles of treatment with hMG and five of these had ovulated on one or more occasions. The clinical summary of the 10 patients is shown in Table 1. The patients were assessed for obesity by the body mass index (BMI) (Keys *et al.* 1972). Nine of the 10 women had a value above 24. All women had patent fallopian tubes and all husbands had semen analyses in the normal range.

Endocrine studies

The hormones assayed included LH, FSH, oestradiol (E2), progesterone (P4) androstenedione (A4), testosterone (T4), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG) and inhibin. The methods for the steroid hormones measured have been described previously (Buckler *et al.* 1989). Inhibin was measured in a heterologous assay system using ^{125}I-labelled bovine inhibin as tracer, an antibovine inhibin antiserum and a human serum standard obtained from women undergoing hyperstimulation (McLachlan *et al.* 1987).

Preoperative sampling consisted of weekly samples for 4 weeks, and then on the morning of surgery. Post operatively, blood was taken on the first post-operative day and then twice weekly for 3 weeks and weekly for 4 weeks or until menses recommenced. Subsequent cycles were monitored for ovulation by collecting 10-h overnight urines for oestrone-1-glucoronide and pregnanediol excretion (Kovacs *et al.* 1985).

Ovarian cautery

The procedure was performed under relaxant general anaesthesia. Laparoscopy was by the routine diagnostic double puncture method using Storz laparoscopy equipment. After insufflation of the peritoneal cavity with carbon dioxide, a 7 mm trocar and cannula was introduced sub-umbilically and a 6·5 mm forward-oblique 30° laparoscope was inserted. This was connected to a conventional cold light source. A second incision was made suprapubically for a 5·5 mm diametertrocar and cannula, to introduce a Semm grasping forcep The patient was placed in the Trendelenberg position and bowel was scooped upwards under direct vision. The ovarian pedicle was grasped with the forcep. A third puncture with a 5·5 mm trocar and cannula was made half way between the umbilicus and the suprapubic incision. Through this another Semm forcep was inserted. Whilst the ovary was being fixed with the first forcep, the second forcep was used to grasp the ovarian capsule. With the enlarged polycystic ovaries which these patients have, the technique is a little difficult and resembled trying to grasp a football with ice tongs. If the forceps were fully opened, it was possible to push one of its jaws through the ovarian capsule and get a better grasp. Once the ovarian tissue was grasped within the jaws of the forceps, a unipolar diathermy current was passed down the forcep. This resulted in cauterization of the ovarian capsule adjacent to the forcep. Great care was taken that no other tissue was burnt. This procedure was repeated 10 times on each of the ovaries. The ovary was released when the tissues appeared to have cooled.

All women were discharged on the morning after surgery. No complications were reported other than mild post-operative abdominal discomfort.

The project was approved by the Human Research (Advisory and Ethics) Committee of Prince Henry's Hospital, and all patients gave informed consent.

Table 1. Clinical summary of the ten patients treated

No	Age (years)	BMI	Outcome
1	27	32·9	Responsive to hMG—pregnant
2	27	32·7	Spontaneous ovulation—pregnant
3	23	29·2	Anovulatory—resistant†
4	39	41·7	Responsive to hMG*—pregnant
5	34	44·2	Spontaneous ovulation
6	26	21·5	Spontaneous ovulation—pregnant
7	32	27·0	Spontaneous ovulation—pregnant by IVF
8	29	33·7	Spontaneous ovulation
9	29	27·7	Spontaneous ovulation
10	39	34·4	Spontaneous ovulation
Mean	30·5	32·5	
(SD)	(5·4)	(6·8)	

*Prior to cautery only one out of five cycles was ovulatory.

†Spontaneous ovulation and pregnancy 18 months later but miscarried

BMI=body mass index

Statistical methods

The changes in each subject's mean hormone and SHBG levels before and after surgery were used as summary measures of the effect of the ovarian cautery, and the significance of the changes were assessed by paired *t*-tests (Matthews *et al.* 1990).

Results

The clinical summary of the 10 women is shown in Table 1. Seven of the 10 women ovulated spontaneously within 8 weeks of surgery as judged by urinary pregnandiol excretion. One patient (no. 6) conceived within 14 weeks of the surgery and has had a healthy male infant; another (no. 2) conceived spontaneously 12 months after cautery and has a normal ongoing pregnancy.

The three women who did not ovulate spontaneously had 0/5, 0/2 and 1/5 ovulatory hMG treatment cycles previously. The first of these women (no. 1) responded to hMG for the first

Table 2. Hormone levels before and after surgery

Hormone	(Normal range)†	Preoperative		Postoperative		Change	
		Mean	(range)	Mean	(range)	Mean	(SE)
FSH (IU/l)	(3·0–6·0)	4·6	(2·5–7·0)	4·8	(3·2–5·7)	0·16†	(0·30)
LH (IU/l)	(3·0–12·4)	17·5	(7·9–43·1)	16·5	(7·1–37·1)	−0·93	(1·77)
E2 (pmol/l)	(150–300)	92·5	(44–499)	74·6	(41–149)	−17·9	(1·54)
P4 (nmol/l)	(0·3–4·8)	1·1	(0·1–3·8)	1·4	(0·2–2·2)	0·30†	(0·40)
DHEAS (nmol/l)	(0·9–11·7)	6·1	(1·4–11·6)	6·5	(1·4–11·6)	0·41†	(0·55)
SHBG (nmol/l)	(20–100)	30·0	(10–96)	30·7	(9–96)	0·70†	(0·87)
A4 (nmol/l)	(2·5–6·5)	4·1	(0·8–6·8)	3·6	(1·0–5·5)	−0·50	(0·33)
T4 (nmol/l)	(1·0–3·3)	2·6	(1·3–4·0)	1·9	(1·1–2·6)	−0·65*	(0·21)
Inhibin (u/l)	(100–1026)	328	(46–1002)	277	(94–462)	−51	(60)

*p=0·011
†Follicular phase

time after surgery and conceived but had an incomplete miscarriage at 8 weeks. Another woman (no. 4) conceived after hMG and was delivered of a child.

One patient (no. 3) remained anovulatory, amenorrheic and resistant to hMG stimulation, but ovulated spontaneously and conceived 18 months later, but miscarried. One patient had a follow up laparoscopy 18 months after the cautery and no adhesions were present.

Changes in hormone levels

The changes in mean levels before and after the operation are summarized in Table 2. FSH and LH showed no significant changes with time. There was a wide range of results for E2 and P4 both before and after the surgery. Subjects 2 and 9 showed some luteal activity preoperatively and, as mentioned above, many ovulated postoperatively. While this clouds interpretation of the analysis, there was no significant change in the pooled mean pre- and post-operative values for these measurements. Testosterone showed a significant fall in mean levels after the operation by approximately 0·65 nmol/l (Fig. 1) Inhibin levels fell in the first 2 weeks after the operation and rose thereafter (Fig. 1). However, overall there was no significant change in the pooled mean pre- and post-operative inhibin levels. The other hormone and SHBG mean results did not change significantly

Discussion

It was encouraging that 7 of the 10 (70%) women ovulated, soon after the surgery. It is noteworthy that most of the women were obese. Furthermore, selection was such that 7 of the 10 women recruited were treatment failures with hMG, having either not responded to stimulation (2 patients) or having ovulated between 1 and 6 times but not conceived (5 patients). It is poss-

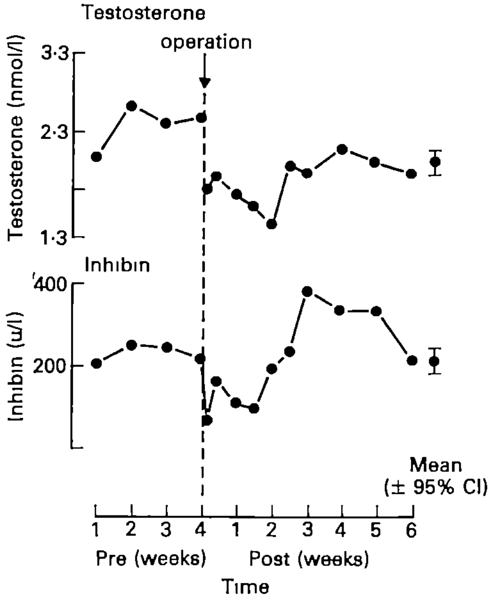

Fig. 1. Changes in mean testosterone and inhibin levels before and after ovarian cautery.

ible that in the latter there has been another barrier to conception, although the basic fertility testing appeared normal. One conceived subsequently by *in vitro* fertilization, supporting this hypothesis. The conversion from hMG resistance (5 previous anovulatory cycles) to hMG responsiveness with conception (patient 1) is reassuring.

There was a predictably high LH to FSH ratio in the pooled pretreatment hormone levels, and plasma oestradiol levels were also low in the early follicular range. Serum androgens were within the normal range, and SHBG below the lower level of normal in 3 of the 10 subjects, again reflecting the subjects' obesity.

The two hormones that changed significantly after cautery were testosterone and inhibin. Whereas testosterone levels fell persistently, inhibin levels fell only transiently, then rose again. this may reflect transient damage to superficially placed follicles, with a consequent fall in inhibin production, but rapid recovery. Although the change in testosterone was statistically significant, the biological relevance is difficult to assess The clinical benefit, despite the lack of a significant change in LH, makes it difficult to find any rationale for the improvement. The frequency of adhesion formation after this treatment is not yet known and only one of our patients has had a subsequent laparoscopy. There have been no reports from other workers about post-operative adhesions in their follow up (Gjonnaess 1984, Greenblatt & Casper 1987). However, the absence of laparotomy and minimal bleeding should make this method much less likely to cause adhesions.

Recent animal studies have shown absence of adhesions with the use of intrapelvic laser surgery (Petrucco 1988). Two recent reports have suggested that results from laser surgery are comparable to those obtained by electrocautery (Huber *et al.* 1988; Daniell & Miller 1989).

The results are encouraging enough to recommend consideration of ovarian electrocautery or laser vaporization before proceeding to ovulation induction with gonadotrophins for women with PCOS. It is normal to check tubal patency by laparoscopy before proceeding to gonadotrophin stimulation, and ovarian cautery during laparoscopy is a relatively simple procedure. Compared with gonadotrophins, the expense of monitoring and the multiple pregnancy rate, ovarian cautery is certainly cost effective. If our initial results showing that some women became more responsive to gonadotrophins after electrocautery are confirmed, then this is another reason for trying the surgical approach before proceeding to gonadotrophins. We plan to undertake a prospective randomized trial of cautery in comparison to gonadotrophin stimulation to assess this suggestion.

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Fetal monitoring with pulse oximetry

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Summary. Continuous fetal monitoring was achieved with a fetal scalp pulse oximetry sensor in 86 labours. The average recorded fetal oxygen saturation in early labour (cervical dilatation < 5 cm) was 68% (SD 13%). At the end of labour (cervical dilatation ⩾ 9 cm) the recorded mean oxygen saturation was 58% (SD 17%). The largest range of readings during a single labour was 81%–11% but this drop was associated with cord compression. The average SD during 1 h of normal labour was 10%. A second group of 40 fetuses was monitored during induction of labour before and after elective amniotomy. Oxygen saturation did not appear to change after amniotomy (mean change −0·4%, SD 1·2%) and there was no difference between mean antenatal or early intrapartum readings. We excluded the amniochorionic membranes as a possible source of data corruption by measuring their in vitro absorption spectra and confirming that they do not preferentially absorb light of either 660 or 940 nm wavelength. Non-invasive pulse oximetry can be used to monitor the fetus before and during labour.

Pulse oximetry has revolutionized the monitoring of anaesthetic and neonatal patients. Oximeters record both heart rate and arterial oxygen saturation (Tremper & Barker 1989) and they may be adapted to derive an estimate of peripheral perfusion (Johnson *et al.* 1989a). Pulse oximeters are a cheap non-invasive method of monitoring and it was a logical advance to adapt this tool for fetal surveillance (Peat *et al.* 1988; Johnson & Lilford 1989; Gardosi *et al.* 1989).

We monitored healthy fetuses continuously during normal labour and in a second study we measured oxygen saturation before the onset of labour through intact membranes.

Subjects and methods

Intrapartum monitoring

We obtained continuous intrapartum scalp pulse oximetry readings from 86 fetuses; all were at term, presenting by the vertex and were monitored by placing the oximetry probe on the scalp during a vaginal examination. Fetuses developing palpable caput formation and meconium staining of the amniotic fluid were excluded, as it is known that these factors may affect the oxygen saturation reading (Johnson *et al.* 1989b and 1990a & b). Other risk factors such as preterm birth, antepartum haemorrhage and twins were excluded. It is difficult to get good scalp readings from curly haired negro babies and therefore all results presented in this paper refer to European full-term babies. Our sample is also biased towards women with epidural anaesthesia (80%) because we felt it was unreasonable to

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obtain consent from women in late and painful labour.

We adapted the Criticare 502 pulse oximeter multisite sensor into a fetal probe. The components of the sensor (Fig. 1) are moulded into a silicone rubber suction cap and mounted in the same plane. The red and infra-red light emitting diodes are 6 and 8 mm respectively from the photosensitive cell and they lie in a bed of carbon paint to prevent light shunting across the probe. The probe, and its trailing suction pipe and electric wires are placed above the cervix on the presenting part of the fetus during a vaginal examination. A low suction pressure of −7 mm Hg is sufficient to ensure apposition and in our experience this leaves no mark on the scalp. The configuration of this probe (probe 1) prevents the electronic components being pressed too firmly against the head even during a contraction (this would empty the vascular bed beneath the probe and distort the signal). The output of the probe was connected to a Criticare 502 pulse oximeter. Initially all the data were recorded on paper but midway through the work the Criticare 502 pulse oximeter was linked to a BBC microcomputer. Every 5 s the computer sampled the oxygen saturation reading to calculate mean oxygen saturation and standard deviation. The pulsatile component of the detected infra red light was continuously recorded on a paper chart recorder as a plethysmograph and the fetal heart rate was simultaneously monitored with a maternal transabdominal Doppler probe from a cardiotocograph recorder (FM6; Sonicaid of Oxford). Data were only accepted by the programme when a reliable sinusoidal plethysmograph was obtained. We also disregarded data when the detected fetal heart rate was not within 10 beats/min of that recorded by the maternal transabdominal Doppler machine. Patients were recruited according to their availability and the intention was to monitor the fetus continuously for as long as possible. Unfortunately signals satisfying the criteria for acceptability were not always obtained for long periods and it was not possible to monitor labours from beginning to delivery. Therefore the subjects have been divided into early labour (cervical dilatation < 5 cm), mid labour (cervical dilatation between 6 and 8 cm) and late labour (cervical dilatation ≥ 9 cm) and comparative analysis of data was performed with two tailed unpaired *t*-test including corrections for more than one analysis. We obtained maternal consent on admission to the labour ward and the study was approved by our local ethics committee.

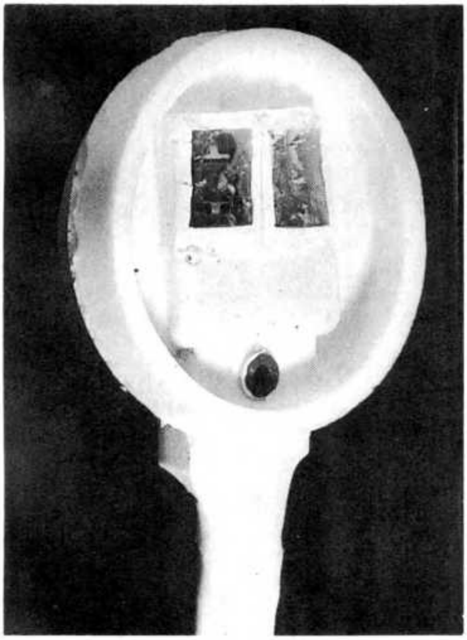

Fig. 1. Fetal pulse oximetry suction probe. External pressure is transmitted to the outer rim, not the sensor.

Antenatal monitoring

Antenatal oximetry was studied in 40 further women scheduled for induction of labour by amniotomy. Readings taken before they entered labour were made with a second probe (probe 2). The geometry of the electronics in this probe is identical with that used during labour but the probe was stripped of excess silicone which formed the suction cap to make it as small as possible so that it could pass through the pregnant cervix before the onset of labour. The probe has to be held on the presenting part manually and obtains one-off readings through intact membranes. Membranes were ruptured and amniotic fluid allowed to drain. Once the fetal head had stabilized a further oximetry reading was obtained.

The theoretical effect of an amniochorionic membrane interface on reflectance pulse oximeter readings was studied by interposing five different membrane specimens between the probe and adult skin. In addition, the light absorption spectrum of five different meconium-free amniochorionic membranes was plotted using a spectrophotometer (Cecil Cambridge 303).

Results

Intrapartum monitoring

At least 145 fetuses were monitored and signals satisfying the acceptability criteria for at least 15 min were obtained in 86. All fetuses were born in good condition with median Apgar score of 7 (range 4–10) at 1 min and 9 (range 6–10) at 3 min. No baby needed specialized paediatric care.

The mean oximetry reading in late labour was lower than the mean in early labour (Table 1). The average standard deviation of oximetry readings for each fetus was 10% (e.g., Fig. 2). The largest range of oximetry readings from a labour that was initially uncomplicated was 81–11%. However, in this labour the drop in oxygen saturation was accompanied by severe cardiotocographic deceleration, and both the fetal heart pattern and oxygen saturation reading improved when the woman changed her position (Johnson & Johnson 1989). The fetus was born by emergency caesarean section and a loop of cord was found by the baby's ear. Fetal oximetry readings increased with maternal oxygen administration in two of seven subjects by 4% and 7%, and they decreased in one woman with hypertonic uterine stimulation (Fig. 3). However, any change in oxygen saturation during a contraction must be interpreted with caution until the precise effect of increasing pressure on an oximetry probe is understood (Johnson 1990).

Antenatal monitoring

The amniochorionic membranes did not affect the oximetry readings. Although it was impossible to obtain continuous oxygen saturation readings during artificial rupture of membranes because of movement interference, readings before and after the amniotomy did not show any significant trend towards an increased or decreased oxygen saturation. The mean change after amniotomy was −0·4% (SD 1·2%; $P = 0{\cdot}8$, paired t-test). The median time from membrane rupture to the second oximetry reading was 4 min. When meconium-free amniochorionic membranes were used as an interface between the probe and adult skin no alteration was obtained in oxygen saturation readings (Mean difference = +0·4%; $n = 5$).

The extinction co-efficient (amount of light absorbed) of the amniochorionic membranes varied according to the thickness of the membrane samples, but there was no difference in the light absorbed at the two wavelengths (660 and 940 nm). The mean ratio of absorbed light at 660 nm to 940 nm was 1·04 ($n = 5$).

Table 1. The average fetal oximetry reading in normal unstimulated labour*

Stage	Cervical dilatation (cm)	Oximetry reading (%)			
		n	mean	(SD)	range
Early labour	< 5	51	68	(13)	11–81
Mid labour	6–8	12	60	(12)	40–80
Late labour	> 9	23	58	(17)	29–81

Comparing early and middle labour with a two tailed unpaired t test including corrections for more than one test, $t = 1{\cdot}8$; $P = 0{\cdot}15$

Comparing early and late labour with the same test, $t = 2{\cdot}7$, $P = 0{\cdot}014$

*Women receiving oxygen or lying on their back are not included

Discussion

Electronic monitoring of fetal heart rate falls far short of the theoretical ideal (Thacker 1987; Steer & Carter 1989) and meta-analysis of nine randomized trials (including 54 000 patients) showed that, at least under trial conditions, it has little advantage over careful auscultation (Grant 1989). Intermittent fetal blood sampling is an inconvenient method of routine intrapartum fetal monitoring, continuous pH electrodes are prohibitively expensive and oxygen partial pressure monitoring is cumbersome and not suf-

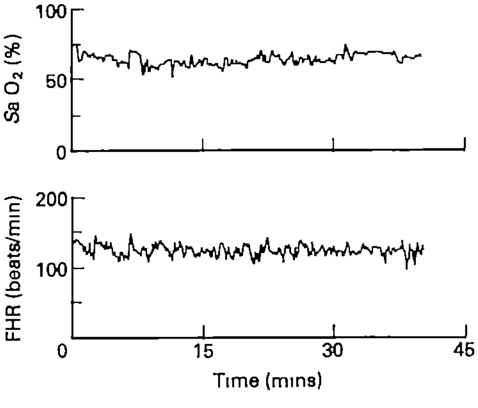

Fig. 2. A typical example of continuous fetal oximetry monitoring recording fetal scalp oxygen saturation (SaO_2) and fetal heart rate (FHR).

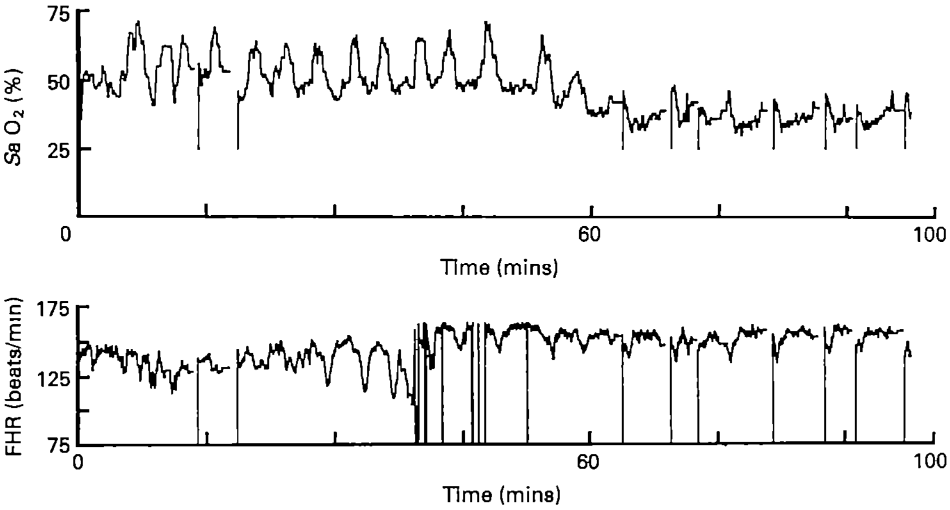

Fig. 3. Arteriolar fetal scalp oxygen saturation (SaO_2) and fetal heart rate (FHR) recorded with probe 1 during a labour initially complicated by oxytocin-induced uterine hyperstimulation (note the general trend in oxygen levels). Gaps represent loss of contact and the vertical lines mark the return of the signal.

ficiently sensitive to be a reliable method of monitoring (Huch *et al.* 1977; Small *et al.* 1989).

We have already shown that deleterious changes in fetal oxygen saturation preceded changes in the fetal heart rate during an acute insult (Johnson & Johnson 1989) and there is some evidence that fetal wellbeing is related to signal strength (Johnson *et al.* 1989a). Oxygenation and acidosis are related to fetal wellbeing and there are specific advantages of recording SaO_2 rather than partial pressure of oxygen (PaO_2).

(i) The Clarke oxygen pressure electrode requires frequent calibration and drift occurs as the anode oxidizes. It necessitates shaving hair, firm fixation techniques are essential and the heated electrode can cause first and second degree burns (Golden 1981).

(ii) The relation of oxygen saturation and partial pressure is defined by the oxygen dissociation curve and in the fetus a small change in PaO_2 is represented by a large change in SaO_2. It is much easier to detect a large change as opposed to a small one and experimental error is relatively more important if small alterations must be measured.

(iii) An increase in hydrogen ion concentration moves the oxygen dissociation curve to the right (the Bohr effect) and this can result in an acidotic and hypoxaemic baby with its PaO_2 in the normal range. However, the SaO_2 will be low.

(iv) 2, 3-diphosphaglycerate also shifts the oxygen dissociation curve to the right and a baby that is chronically hypoxaemic or acidaemic may have a normal PaO_2 but its oxygen saturation will be low

(v) Pulse oximeters are routinely used to monitor the patient's wellbeing in anaesthetic and neonatal practice. Their accuracy has been established in these circumstances and unlike oxygen tension (PaO_2) monitors they respond rapidly to changes in the oxygen content of the blood.

Labour is associated with a decline in fetal oximetry readings. One explanation for this observation is that as the head descends, scalp congestion increases. An increase in venous pulsation and accumulation of extracellular fluid in the scalp may cause the oximeter to display low values. However, the deleterious effect of labour on the fetus has been observed previously using oxygen tension and pH probes (Simkovich 1981; Modanlou *et al.* 1973; Rooth 1987) and therefore it is likely that our observation is a true reflection of fetal oxygenation.

A mean oximetry value of 68% in healthy fetuses during early labour and a value of 58% before birth are somewhat higher than values derived from pH and PaO_2 data in the existing literature. The healthy fetus at term is born with an umbilical vein blood oxygen saturation of between 40% and 70% (Smith 1959) and as umbilical vein blood mixes with deoxygenated blood from the inferior vena cava before entering the fetal carotid artery, scalp pulse oximetry readings should be below this range. The slightly higher fetal oximetry readings reflect the fact that oximeters are empirically calibrated using a calibration curve constructed from transmission probes on healthy adults over an oxygen saturation range of 100%–70%. The oximeter's microprocessor unjustifiably extrapolates this curve at lower levels of saturation and therefore reflectance readings from the fetus will need small calibration adjustments to take into account fetal Hb, reflectance techniques and the low oxygen levels. However, a change in oximetry readings will still reflect a change in fetal oxygenation.

The amniochorionic membranes do not affect oximetry readings. Consequently oximetry readings taken antenatally through intact membranes reflect fetal oxygen saturation before the onset of labour.

We have established that reflectance oximetry readings are affected if there is an interface between the probe which preferentially absorbs one of the two light wavelengths (Johnson *et al.* 1990a), but analysis of the absorption spectra of the in-vitro amniochorionic membranes confirms that there is no preferential absorption of either red or infra-red light. As membranes absorb each wavelength of light equally, preferential shunting of one wavelength will not occur through the membranes, although the total light transmitted will be decreased. The oximeter is equipped with an 'auto gain' and this compensates for the reduction in detected light by increasing the power output to the diodes. Moreover, if the amniochorionic membranes affect the oximetry reading, we would have expected a systematic increase or decrease in readings after amniotomy. This was not observed. Readings obtained before and 4 min after artificial rupture of the membranes differed on average by only 0·4% The lack of any significant changes in oxygen saturation values does not support the theory that membranes provide a bag cushioning the fetus and protecting it from hypoxaemia. However, hypoxic changes could have occurred in the 4-min period immediately after amniotomy where we were unable to monitor the fetal oxygen saturation because of movement of the fetal head. Furthermore, there is a wide range in readings and small changes in oxygenation could have been obscured in this wide variance. Any such effect would be very small indeed, because comparison of pre- and post-amniotomy readings within patients (paired t-test; $P = 0{\cdot}8$) showed no significant change.

Obstetricians are continuing to search for better means of fetal surveillance, and the development of a reflectance pulse oximetry probe prompted us to monitor fetal oxygen saturation continuously in the hope of using it as a new tool to predict fetal distress. Although fetal pulse oximetry is limited by caput, fetal hair, a wide normal range, poor calibration and difficulties in getting signals every time, we have shown that fetal pulse oximetry can work. In the future, changes in the oximetry reading may help the obstetrician predict fetal distress and antenatal oximetry stress testing may identify fetuses with poor placental reserve before labour.

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Coagulation studies in the syndrome of haemolysis, elevated liver enzymes and low platelets

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Summary. The presence of disseminated intravascular coagulation (DIC) in the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) is debated. We assessed the occurrence of decompensated and compensated DIC (using predefined criteria) in 15 consecutive nulliparous pregnant patients with gestastional hypertension combined with the HELLP syndrome and in 12 consecutive nulliparous controls with pregnancy induced hypertension (PIH) but without the HELLP syndrome. A combination of routine coagulation assays revealed the absence of decompensated DIC in all studied patients. However, using more specific and sensitive coagulation assays, compensated DIC was observed in all HELLP patients and in three patients in the control group. The mean values of antithrombin III, thrombin-antithrombin III complexes and protein C in the HELLP and the control group were 66 vs 87% (*P*=0·0004), 21 *vs* 8 ng/ml (*P*=0·0008) and 57 *vs* 90% (*P*=0·0018) respectively. We conclude that HELLP patients show evidence of compensated DIC which may have pathophysiological significance for the observed organ damage.

About 5–10% of the women with pregnancy induced hypertension (PIH) will develop a syndrome characterized by haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) (Pritchard *et al.* 1954; Weinstein 1982; Sibai *et al.* 1986). Since its first description, the occurrence of disseminated intravascular coagulation (DIC) as a part of this syndrome has been debated. Many investigators, using a set of routine coagulation tests for the detection of DIC have rarely observed abnormalities and therefore concluded that DIC is absent in the syndrome (Gibson *et al.* 1982; Weinstein 1985; Beller *et al.* 1985; Burrows *et al.* 1987).

However, these routine screening tests may be too insensitive (Feinstein 1982) and indeed other workers, using more sensitive methods, have provided evidence suggesting coagulation activation (Greer *et al.* 1985; Weenink *et al.* 1985; Weiner 1988).

The coagulation system can be viewed as a series of linked proteolytic reactions, finally resulting in a fibrin clot. In this process thrombin is considered the key enzyme which catalyzes the conversion of fibrinogen to fibrin, while antithrombin III and protein C are the major physiological inhibitors of the system. Initially, upon activation of the coagulation cascade, antithrombin III and protein C will inhibit thrombin action and consequently thrombin-antithrombin III complexes will be formed and the plasma concentrations of antithrombin III and protein C

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may decrease, without changes in the overall coagulation tests (defined as compensated DIC). If the trigger continues, the inhibitory system will become exhausted and full blown coagulation activation with consumption of all clotting factors will occur (designated as decompensated DIC).

The aim of this study is to assess the occurrence of compensated and decompensated DIC in a series of consecutive HELLP patients compared with a non-HELLP hypertensive control group.

Patients and methods

Blood samples were obtained upon admission from 15 consecutive nulliparous women in the third trimester who had PIH and the HELLP syndrome. The control group consisted of 12 consecutive nulliparous women in the third trimester who had PIH only.

Both patient groups were admitted to the Department of Obstetrics of the Academic Medical Centre, University of Amsterdam, and studied prospectively.

The HELLP syndrome was considered to be present when the platelet count was below 100 × 10^9/l, serum pyruvic transaminase (SGPT) was above 50 U/l and the lactic dehydrogenase (LDH) was above 180 U/l, in the absence of any other non-obstetric disease explaining these findings. PIH was defined as a diastolic blood pressure $\geqslant$ 90 mm Hg and a rise of $\geqslant$ 20 mm Hg during pregnancy measured on at least two different occasions.

All patients were treated with rest in bed and salt restriction. Methyldopa was prescribed in two patients in each group. No anticoagulants or anti-platelet drugs were used. Patients with placental abruption, a dead fetus *in utero* or in labour were excluded in both groups. Informed consent was obtained from all patients

Blood collection

Blood was obtained from an antecubital vein by a 19-gauge butterfly needle and collected in plastic tubes containing either trisodium citrate-didydrate 3.2% (1 vol to 9 vol blood) or solid K_2EDTA (1·5 mg/ml of blood). Plasma was prepared by centrifugation at 1600 *g* for 20 min at room temperature and stored at −40°.

Coagulation studies

Routine coagulation assays for DIC. The activated partial thromboplastin time (APTT), the prothrombin time (PT), plasma concentration of fibrinogen, the ethanol gelation test, platelet count and the fibrin/fibrinogen degradation products (FDP/fdp) were measured according to standard techniques (Thomson 1980).

Specific coagulation assays for DIC. Plasma antithrombin III activity was measured using a chromogenic substrate method (Peters *et al.* 1982). Thrombin-antithrombin III complexes were measured with an enzyme-linked immunoassay (Hoek *et al.* 1988). Normal values for third trimester pregnancy range from 4·5 to 9·6 ng/ml (de Boer 1989). Protein C activity was measured using a chromogenic assay according to the manufacturer's instruction (Behringwerke AG, Marburg FRG). Concentrations of antithrombin III and protein C were expressed as percentage of a reference pool of plasma from 40 healthy volunteers (20 men, 20 women). Normal values ranged between 80 and 120%.

Definitions

Decompensated DIC. This was considered to be present if three of the following five routine coagulation tests were abnormal, i.e., activated partial thromboplastin time above the normal range (> 36 s), prothrombin time prolonged > 1·5 s over control, ethanol gelation test positive, fibrin/fibrinogen degradation products over 40 mg/l and plasma fibrinogen less than 1·5 g/l.

Compensated DIC. This was defined as two or more abnormal specific coagulation tests and a set of normal routine coagulation tests. This implied antithrombin III or protein C levels < 80% and thrombin-antithrombin III complexes over 9·6 ng/ml.

Statistical analysis

The Mann-Whitney *U* and the χ^2 test (both two sided) were used to test for differences in measures of location. A *P* value of < 0·05 was considered statistically significant.

Results

The clinical and laboratory characteristics of both groups of hypertensive nulliparous pregnant women at entry are summarized in Table 1. The mean gestational age at presentation in the patients with the HELLP syndrome was 5 weeks less advanced than in those without the HELLP

Table 1. Characteristics at entry of 15 patients with pregnancy induced hypertension combined with the HELLP syndrome and 12 patients with pregnancy induced hypertension without the HELLP syndrome

Factor	HELLP (*n* = 15) Mean (SD)	Range	non-HELLP (*n* = 12) Mean (SD)	Range	*P*
Maternal age (years)	27 (3·5)	21–32	27 (5 8)	18–38	NS
Gestational age (weeks)	31 (3·3)	26–37	36 (3 8)	30–40	0·006
Diastolic blood pressure (mm Hg)	108 (9·4)	90–125	108 (8·1)	100–125	NS
Proteinuria (g/24 h)	5 (6·0)	0–18	2 (1·8)	0–6	NS
Serum pyruvic oxalo-acetate transaminase (U/l)	254 (258)	60–1089	17 (11)	6–39	0·00001
Lactic dehydrogenase (U/l)	470 (292)	195–1145	104 (22)	77–144	0·00001

NS = not significant

syndrome. The observed diastolic blood pressures were identical in the two study groups. In both groups three patients had no proteinuria > 0·3 g/24 h at entry, but in the control group two patients developed proteinuria in the further course of pregnancy. The mean level of proteinuria was not significantly higher in the HELLP group than in those with PIH alone.

The mean gestational ages at delivery in the HELLP and non-HELLP patients were 33 weeks (SD 3·8) and 38 weeks (SD 3·5) respectively (*P* = 0·006); the mean birthweights in the groups were 1401 g (SD 628) and 2402 g (SD 910) (*P* = 0·001). Four stillbirths occurred in the HELLP group, whereas none was observed in the non-HELLP patients Four women in each group were delivered by caesarean section, all because of fetal distress

In Table 2 the coagulation factors of the two groups are shown. The results of the routine coagulation tests for DIC were not clearly different between the two study groups. The plasma fibrinogen concentrations were identical and showed levels seen in normal pregnancy. Half of the HELLP patients showed modest prolongations of the APTT and small increases of fibrin/fibrinogen degradation products. Only one patient in the HELLP group had an abnormal ethanol gelation test None of the study patients had three or more abnormal routine coagulation tests signifying decompensated DIC.

In contrast, marked and highly statistically significant differences between the HELLP and the non-HELLP group were observed with the specific set of coagulation tests for DIC, i.e., plasma concentrations of antithrombin III, thrombin-antithrombin III complexes and protein C, indicative of compensated DIC. The individual values of these components are shown in Fig 1. In all 15 HELLP patients two or more

Table 2. Coagulation factors at entry in patients with pregnancy induced hypertension with or without the HELLP syndrome

Factor	HELLP (*n* = 15)	non-HELLP (*n* = 12)	*P*
Fibrinogen (g/l)	4·5 (0·7) 3·3–6·0	4·4 (0·6) 3·3–5·3	NS
Prolonged APTT (*n*)	7	0	0 021
Prolonged PT (*n*)	1	1	NS
Fibrin/fibrinogen degradation products > 40 mg/l (*n*)	8	1	0 04
Positive ethanol gelation test (*n*)	1	0	NS
Platelet count (× 10^9/l)	44 (24) 18–88	195 (65) 101–335	0·00001
Antithrombin III (%)	66 (16) 27–85	87 (11) 62–109	0·0004
Thrombin-antithrombin III complexes (ng/ml)	21 (12) 5–44	8 (2) 4–12	0·0008
Protein C (%)	57 (22) 23–95	90 (21) 55–121	0·0018

Results are mean (SD) values and range or numbers of patients with an abnormal coagulation test as appropriate
APTT = activated partial thromboplastin time
PT = prothrombin time.
NS = non significant

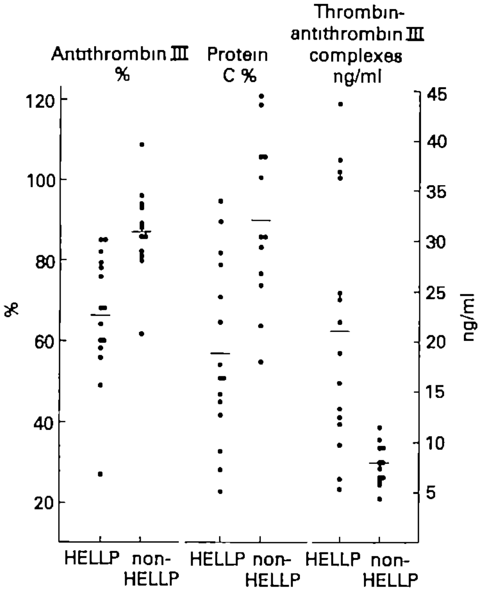

Fig. 1. Plasma concentrations of antithrombin III, protein C and thrombin-antithrombin III complexes at entry of 15 patients with pregnancy induced hypertension combined with the syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP) and in 12 patients with pregnancy induced hypertension without the HELLP syndrome (non-HELLP).

of the specific coagulation assays were abnormal, while in eight patients of the non-HELLP group all three tests were normal. Only three patients in this group had two abnormal test results.

Discussion

The HELLP syndrome is reported to be associated with a high perinatal mortality (8–40%) and a significant maternal morbidity (Weinstein 1982; MacKenna *et al.* 1983; van Dam *et al.* 1989) The pathophysiological mechanism of this syndrome is incompletely understood. Currently endothelial/trophoblastic dysfunction in the uteroplacental system is considered to play a central role in the initiation of the syndrome (Wallenburg 1988, Roberts 1989). It is controversial whether DIC coexists in the syndrome.

Using a set of sensitive and specific coagulation assays our study provides convincing evidence that compensated DIC is present in all HELLP patients. Interestingly, none of these patients met the criteria for the presence of decompensated DIC, thereby confirming earlier observations (Weinstein 1985; MacKenna *et al.* 1983) Moreover, preliminary results of longitudinal testing in a subset of five HELLP patients revealed that these coagulation abnormalities remained rather constant over time (days), suggesting a continuous mild trigger of the coagulation system. In contrast, in the non-HELLP hypertensive control group only three of the 12 patients had compensated DIC.

The observed coagulation activation in the HELLP patients may, however, still result in intravascular fibrin deposition, in particular if the stimulus for activation continues for a period of days. Indeed fibrin deposits have been observed in the liver, kidney and placenta of these patients (Aarnoudse *et al.* 1986; Hill *et al* 1989; Wallenburg 1987) Therefore, it is interesting to speculate that compensated DIC is an important causal factor in the liver-, kidney- and placental dysfunction seen in the syndrome.

How can we explain the observed haemostatic abnormalities? Several investigators have provided evidence that the decreased number of platelets in HELLP patients probably results from local platelet aggregation in the uteroplacental vasculature due to impaired prostacyclin synthesis in the cells lining the uteroplacental arteries (Walsh 1989). During this primary event of platelet aggregation small amounts of thrombin will be generated. We hypothesize that this thrombin is improperly neutralized by the natural anticoagulant mechanisms. The major inhibition of thrombin occurs at the endothelial cell surface where endogeneous heparin-like molecules and antithrombin III effectively bind thrombin (Bauer & Rosenberg 1987). In the case of endothelial cell dysfunction or damage at the site of uteroplacental arteries, the generated thrombin may be insufficiently inhibited. Consequently small concentrations of the enzyme may enter the systemic circulation which is then reflected in the observed compensated DIC and possibly fibrin deposits in different organs seen in HELLP patients.

Hepatic dysfunction as a possible cause for the low levels of antithrombin III and protein C is not excluded but unlikely, taking into account the normal values of the prothrombin time and the concommitent increase in thrombin-antithrombin III complexes in these compensated DIC patients.

Whether therapeutic intervention against the observed coagulation activation will favourably influence the course of the HELLP syndrome remains to be demonstrated. The administration of heparin has been reported only in small series of patients and was not effective (Howie *et al.* 1975). Administration of anti-platelet agents has proven to be effective as a prophylactic regimen in high risk patients, but has not been administrated in HELLP patients (Wallenburg *et al.* 1986).

In summary we conclude that using sensitive and specific assays for the detection of coagulation activation, compensated DIC was invariably present in HELLP patients and may be an important feature in the pathogenesis of the clinical picture.

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Fetal crown-rump length values in the first trimester based upon ovulation timing using the luteinizing hormone surge

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Summary. Fetal crown rump length (CRL) was measured weekly in 33 singleton pregnancies that were established after in vitro fertilization, gamete intrafallopian transfer or natural intercourse in monitored infertility treatment cycles. The time of the luteinizing hormone surge or hCG administration was known for all of them. There was no difference in CRL between the different infertility treatment groups. CRL measurements from this and a similar study where gestational age had been based on the time of ovulation were compared with the CRL measurements from pregnancies where the gestational age had been calculated from the last menstrual period. The CRL was found to be generally smaller in the studies based on ovulation timing and the difference was statistically significant at one time point. This suggests that there is a need for a gold standard in obstetric ultrasound, measurements being based on the gestational age as calculated from the unequivocal date of conception, rather than the last menstrual period.

The original studies of fetal crown-rump length (CRL) in the first trimester of pregnancy, which are widely used to confirm the length of gestation, were based upon the last menstrual period (LMP) in normal menstrual cycles (Robinson & Fleming 1975, Pederson 1982, Drumm *et al.* 1976). This is subject to errors of recollection and cycle irregularity (Rossavik & Gibbons 1985) so that the recorded LMP may only be reliable (as defined by a normal LMP, certain date of LMP, and regular menses) in 18% of pregnancies (Hertz *et al* 1978). Studies of fetal morphological development have found that embryo maturity correlated highly with gestational age based on LMP, but that individual specimens showed substantial variability (SD 10·5 days) (Moore *et al.* 1981).

It has been suggested, to avoid circularity, that the only acceptable 'gold standard' against which to assess the accuracy of ultrasound in estimating gestational age is the actual length of gestation, which should be calculated from an unequivocal, directly known date of conception (Chalmers 1985).

Crown-rump length tables have been described in pregnancies conceived in cycles monitored with basal body temperature charts (Selbing & Fjallbrant 1984), and in pregnancies where ovulation has been detected using a mixture of a mid-cycle leuteinizing hormone (LH) surge in urine, ultrasound detection of follicular collapse and basal body temperature (MacGregor *et al.* 1987). In the latter study (MacGregor *et al* 1987), the findings suggested that when CRL values from previous studies based upon men-

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Table 1. Comparisons of studies of crown-rump-length (CRL) estimation

Study	Year of publication	Equipment	Basis for calculation of gestational age	CRL (mm) at gestational age (days) 49	56	63	70	77	Average difference (days)*
Robinson *et al.*	(1975)	Diasonograph B mode	LMP in normal cycles	10	16	24	33	43	−3·0
Drumm *et al.*	(1976)	Diasonograph B mode	LMP in normal cycles	10	17	24	32	42	−2·8
Pedersen *et al*	(1982)	Diasonograph B mode	LMP in normal cycles	10	16	23	31	41	−2·5
MacGregor *et al*	(1987)	'Dynamic imaging'	LH surge, basal temp, follicular collapse	–	12	21	31	41	−0·5
Present study		Diasonics DRF_1 (real time)	LH surge or hCG administration	7	12	21	29	39	–

* Average difference in days, if gestational age is estimated from CRL, between the present series and the other listed studies.

strual age were compared to their values based upon ovulation data, there was a mean difference of 3.2 days (SD 3·9 days) when compared to the study by Robinson (1975), and 3·5 days (SD 4·0 days) when compared to data from Drumm *et al.* (1976), suggesting that charts based upon menstrual data may underestimate the true gestational age by several days.

As part of an assisted reproduction programme, we took the opportunity to study this concept further using a known date of conception.

Methods and results

In a reproductive endocrinology unit the opportunity was taken to examine 33 patients who had participated successfully in the various infertility programmes. These included 13 women receiving in-vitro fertilization (IVF) and six receiving gamete intrafallopian transfer (GIFT), both of which included ovarian stimulation with clomiphene citrate (Merrell Pharmaceuticals) and Pergonal (human menopausal gonadotrophin hMG–Serono). In addition, the study included 14 women who had conceived in spontaneous cycles.

In the IVF and GIFT cycles, ovulation was stimulated by the administration of human chorionic gonadotrophin (hCG) and the date of this was taken as equivalent to the date of the LH surge. In the spontaneous cycles serum LH was monitored daily. When the LH surge was detected the woman was treated with insemination, or had natural intercourse.

After an elevated serum hCG level was detected, the woman was invited to attend the unit for weekly ultrasound scans until 13 weeks gestation. Abdominal scans were performed using the full bladder technique (Donald 1963). A total of 131 CRL observations were completed on this group of 33 women all of whom had normally developing, singleton pregnancies. The mean of three CRL measurements was taken at each visit. The length of gestation was not known by the ultrasonographer. The ultrasound scanner used was a Diasonics DRF1 sector scanner.

The date of the LH surge or hCG administration was known for each woman, and was taken as 'day 14' of gestational age to enable comparison with data derived from the LMP in normal cycles Day 14 was chosen on the basis that the LH surge occurs on a median of 12·94 days (29% confidence interval 8·2 to 20·5 days) of the menstrual cycle (Lenton and Landgren 1985). The median time from the LH peak to ovulation is 16·5 h (95% CI 9.5 to 23 h) (WHO 1980). Ovulation therefore occurs most frequently on Day 14 (the 13th day) in natural cycles. Ovulation occurs 37 h after hCG administration (Edwards & Steptoe 1975).

The last line of Table 1 shows the mean CRL in our series at 49, 56, 63, 70 and 77 days, adjust-

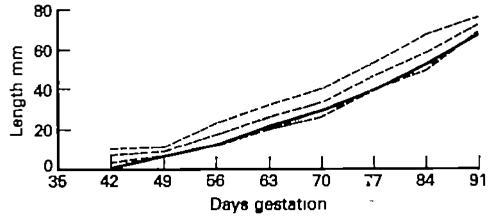

Fig. 1. Mean crown rump length by gestation based on conceptual data from the present study (▬ mean) and menstrual data derived from Robinson & Fleming (1975) (- - - - mean ±2SD).

ment for missing data being made by use of the multiple classification option in the SPSS-X ANOVA procedure, modelling the dependence of CRL on subject and week. Each of these means should be regarded as accompanied by a SD of 4.7 mm based upon a components of variation analysis.

First, the possibility that CRL in the three treatment groups might be different was examined in order to justify the pooling of data. The rates of CRL growth and the absolute values week by week were closely similar, again using non-orthogonal ANOVA.

The pooled CRL data from this study based upon ovulation timing (conceptual data) were then compared with the tables compiled by Robinson & Fleming (1975) based upon the LMP (menstrual data) (Fig. 1). Unpaired *t*-tests comparing the two samples were then performed for each weekly epoch from 56 to 84 days. The direction of the difference generally suggested a smaller CRL in our series, though statistical significance at the 0·05 level was only found at one time point, day 70 (Fig. 1).

The studies based upon the LMP and studies where the time of ovulation had been assessed from a mixture of urinary assays for LH, ultrasound detection of follicular collapse and basal body temperature observations (MacGregor *et al.* 1987) were compared with the present study (Table 1).

All the studies followed a similar growth rate but data based upon the LMP were consistently 2–4 days ahead of the CRL data derived from the women in this study, where the time of ovulation was known. There was no difference between CRL growth rates in the present series based upon ovulation timing and the one similar study (MacGregor *et al.* 1987) (Table 1).

Discussion

The difference of 2–4 days in CRL observations between the data in this series and the values from the original studies (Robinson and Fleming 1975; Drumm *et al.* 1976; Pederson 1982) is similar to the difference found in a previous study of CRL observations where gestation was based upon various methods of ovulation timing (MacGregor *et al.* 1987). The reason for this is unknown.

Population differences may account for some variation since although both groups were young white European women, one group came from Glasgow in the early 1970s and the group used for comparison were Australians in the mid 1980s. The difference, however, operates in a direction contrary to that which one would expect if factors based upon nutrition or standard of living were responsible. It is possible that the original group from Glasgow were not typical of the general population in that they had all attended early in pregnancy to be included in the study.

The fertility status of the women being treated may play a part, although this seems unlikely since both this study and previous studies (MacGregor *et al.* 1987) have shown no difference in CRL growth between pregnancies conceived in natural cycles which one would expect to be comparable to the normal, and those resulting from assisted conception techniques—ovulation induction, IVF and GIFT. Although ovulation induction with hMG has been shown to slow gestation sac growth (Mayden *et al.* 1986), no such effect has been described for fetal growth.

The difference in results cannot be explained by technology improvements (Adam *et al.* 1979), but it has been postulated that early fetal growth may follow a linear rather than a curved path (Rossavik *et al.* 1988) and this may explain our findings.

Since the recollection of the LMP in a 'normal' cycle may not be as reliable a basis for estimation of gestational age (Hertz *et al.* 1978; Moore *et al.* 1981) as a monitored LH surge, or ovulation induced by administration of hCG, it is possible that the mean difference of 3·0 days in this study and 3·2 days in a previous study (MacGregor *et al.* 1987) may have been caused by a systematic error in the womens' recollection of their LMP. An alternative explanation includes the possibility that in the earlier studies the women tended to have a shorter follicular phase causing earlier ovulation and thus projecting the fetuses several days ahead in crown-rump length.

We have followed the usual practice of presenting summary statistics for the distribution of CRL at each of a number of gestational epochs. A referee has pointed out that the correct approach, very rarely adopted, is to calculate a curve based on the mean length of gestation for a given CRL but we have not done this for two reasons. (i) The main aim of the study was not to be normative, the sample size is not sufficient for that, but to determine the degree of comparability with LMP-based series, which have used the usual method. (ii) In many instances the application of results of normative series is by construction of centile charts, in which interest centres on progression rather than a single time point. The way to tighten up this procedure is to adapt statistically accepted quality control methods (Newcombe 1988).

In summary, this small study reiterates the need for a 'gold standard' for ultrasound measurements where the actual length of gestation is known, since it confirms that a difference of 3 days exists between CRL observations based upon ovulation timing in infertility patients (MacGregor *et al.* 1987) and those based upon the LMP (Robinson & Fleming 1975; Drumm *et al.* 1976; Pederson 1982). These differences are probably not large enough to affect the calculation of the expected date of delivery to a degree that is clinically important, but a discrepancy of 3 days at 6–7 weeks gestation in an infertility pregnancy, where the date of conception is known, may be large enough to cause concern and in this situation it might be preferable to use CRL tables based upon ovulation timing.

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Ratio of immunochemically determined amniotic fluid acetylcholinesterase to butyrylcholinesterase in the differential diagnosis of fetal abnormalities

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Summary. A total of 111 amniotic fluid samples, clear or blood stained, with elevated levels of alpha-fetoprotein and acetylcholinesterase was analysed by immunoassays specific for acetylcholinesterase and butyrylcholinesterase and the acetylcholinesterase/butyrylcholinesterase-ratios determined. Samples from 40 pregnancies associated with anencephaly, 47 pregnancies associated with open spina bifida or encephalocele and six pregnancies with fetal intrauterine death or miscarriage all had ratios of >0·14. All 11 pregnancies with fetal ventral wall defects had ratios <0·14 as had four pregnancies with normal outcome and elevated levels of alpha-fetoprotein and acetylcholinesterase. Three fetuses with both open spina bifida and ventral wall defects were associated with ratios above 0·14. These results suggest that immunochemical determination of acetylcholinesterase and butyrylcholinesterase can be used to distinguish pregnancies complicated by anencephaly, open spina bifida, encephalocele and miscarriage from those with ventral wall defects and samples with false positive elevated levels of alpha-fetoprotein and acetylcholinesterase. The procedure is accurate and simple to carry out and well suited to routine use in a clinical chemistry laboratory.

Determination of amniotic fluid acetylcholinesterase (AChE; EC 3.1.1.7) is a well established procedure in the antenatal diagnosis of fetal malformations, especially open neural-tube defects (NTD) (Report of the Collaborative Acetylcholinesterase Study 1981). AChE is, however, not specific for open NTD. Elevated amniotic fluid AChE is also associated with fetal ventral wall defects (Wald *et al.* 1980), miscarriage and blood contamination of amniotic fluid samples, especially contamination with fetal blood (Report of the Collaborative Acetylcholinesterase Study 1981).

Previous studies have shown that, using polyacrylamide gel electrophoresis (PAGE test) for AChE determination in amniotic fluid samples not visibly contaminated with blood, NTD can usually be distinguished from ventral wall defects by a densitometric scan ratio of AChE

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and butyrylcholinesterase (BuChE; EC 3.1.1.8) (Goldfine *et al* 1983; Wald *et al.* 1984). In pregnancies with fetal NTD, amniotic fluid AChE derives from cerebrospinal fluid which contains insignificant amounts of BuChE. In contrast, with fetal ventral wall defects the level of BuChE in amniotic fluid is higher, probably due to release of BuChE from intestinal smooth muscle, whereas AChE is secreted from intestinal nerve plexes (Appleyard & Smith 1989).

A recent study has compared the performance of the PAGE test and a monoclonal antibody based enzyme antigen immunoassay (immunoassay) for AChE quantitation (Rasmussen Loft *et al.* 1990). The two procedures were found to be equally effective, but in contrast to the PAGE test, the immunoassay could not be used for the differential diagnosis of ventral wall defects and NTD.

The aim of this study was to apply simple and accurate immunoassays on amniotic fluid samples with elevated levels of alpha-fetoprotein (AFP) and AChE to determine the ratios of AChE to BuChE (AChE/BuChE-ratio) for the purpose of differential diagnosis of NTD and ventral wall defects.

Subjects and methods

Samples

Amniotic fluid samples collected between the 14th and the 24th weeks of gestation at different Danish hospitals between 1980 and 1989 have been stored at −20°C. Samples ($n = 111$) with an elevated level of AFP (above two times the median) and AChE (Rasmussen *et al.* 1989) were selected for this study and analysed again for AChE. The samples were from pregnancies associated with the following conditions: 40 with anencephaly, 47 with open spina bifida or encephalocele, three with open spina bifida together with ventral wall defect, six from pregnancies ending in intrauterine fetal death or miscarriage, eleven with open ventral wall defects without NTD and four from normal pregnancies without fetal malformations. Whether the samples were clear or blood stained was recorded and for blood stained samples it was further recorded whether they became clear or remained discoloured after centrifugation.

AChE activity measurement

Amniotic fluid AChE activity, expressed in nkat/l (nmol of substrate hydroyzed per s/l), was determined by an immunoassay using the monoclonal antibody 4F19 (kindly contributed by Novo BioLabs, Novo Industry A/S) (Rasmussen *et al.* 1989); between-run coefficient of variation has been reported to vary between 3% and 6% for the measured range of activities.

BuChE activity—calibration

For calibration of the BuChE immunoassay a 40-donor serum pool was used. BuChE activity of the serum pool was measured at 25°C using the substrate buffer described below and absorbance read at 405 nm (Ellman *et al* 1961); an enzyme activity of 10·86 nkat/l was found. Calibrators of 217, 163, 109, 55, 27, 11 and 5 nkat/l were used in the analysis.

BuChE activity measurement

Using a modification of the procedure for AChE quantitation, BuChE was measured employing a BuChE specific monoclonal antibody (HAH 2–4, Hybridoma Laboratory, Statens Seruminstitut, DK-2300 Copenhagen). To each well of a microtitre plate (Nunc-Immuno plate maxisorp, A/S NUNC, Kamstrup, DK-4000 Roskilde) was added 100 μl sodium phosphate buffered saline (PBS), 10 mmol/l Na-phosphate, pH 7·2 with 145 mmol/l NaCl, containing 2 mg HAH 2–4 monoclonal antibody/l The plate was incubated overnight at 4°C. After coating the plate was washed three times with washing buffer (PBS, pH 7·2 containing 0·05% (v/v) Tween-20 (Merck, Art. 822184). Then 75 μl washing buffer and 25 μl sample, control or calibrator, was added in duplicate and the plate incubated for 2 h at room temperature on a shaker (Titertek, Flow Laboratories Ltd., Woodcock Hill, UK). After three further washes with washing buffer the bound enzyme activity was measured using the following substrate buffer: 100 μl 100 mmol/l sodium phosphate buffer, pH 7·4, containing 10 mmol/l butyrylthiocholine iodide and 0·5 mmol/l 5,5'-dithio-bis-(2-nitrobenzoic acid) (Boehringer Mannheim, Art. 238 007 and 104 477, respectively) was added to each well and the plate incubated, protected from light, for 30 min at room temperature on the shaker. The plate was then read on an EAR 340 FW SLT Easy Reader (SLT-Labinstruments, Groedig/Salzburg, Austria) using the dual wavelength mode, 405 nm minus 620 nm. Correction for

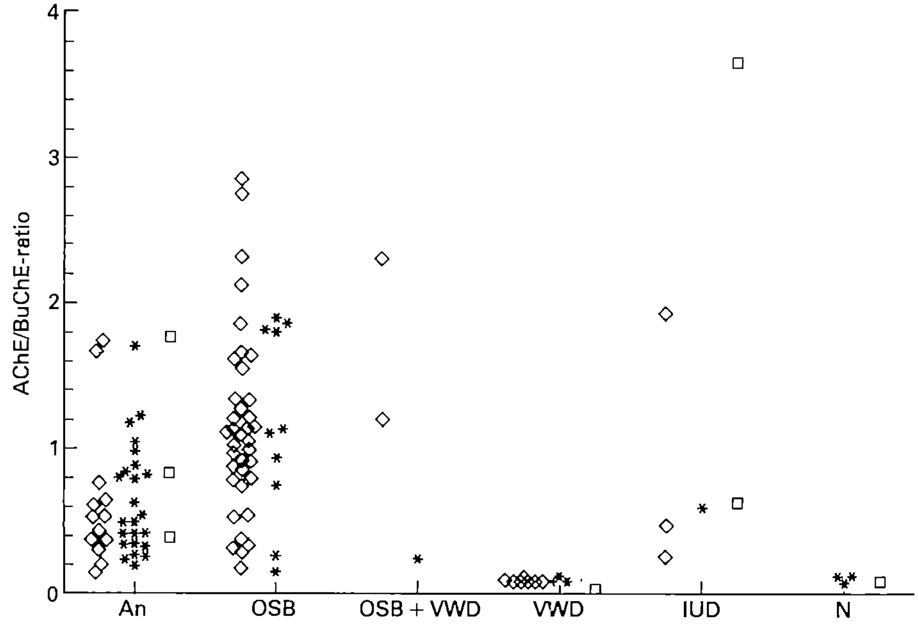

Fig. 1. Acetylcholinesterase (AChE): butyrylcholinesterase (BuChE)-ratios for anencephaly (An), open spina bifida or encephalocele (OSB), open spina bifida together with ventral wall defect (OSB + VWD), ventral wall defect (VWD), intrauterine fetal death or miscarriage (IUD) and unaffected normal pregnancies (N), for clear samples (◇) and bloodstained samples becoming clear (*) or remaining discoloured (□) after centrifugation.

background was performed on each plate. BuChE activities were calculated on the basis of the absorbance at 405 nm by the RIA-calc program (LKB-Wallac Oy, Turku, Finland) using the smoothed spline algorithm. AChE/BuChE-ratios were derived from the measured AChE and BuChE activities. Using different controls between-run precision has been determined; for the measured range of BuChE activities a coefficient of variation of about 5% has been found.

Results

Distributions of AChE and BuChE activities and of AChE/BuChE-ratios are shown in Table 1; within each diagnostic group the results are given separately for clear samples and blood stained samples becoming clear or remaining discoloured after centrifugation. Using AChE or BuChE results, differential diagnosis of ventral wall defects and NTD is not possible. In contrast, the AChE/BuChE-ratios (Fig. 1; Table 1) found in pregnancies with anencephaly or open spina bifida were all ≥0·15 for both clear and blood stained samples. Three pregnancies with fetal open spina bifida as well as ventral wall defects and six pregnancies ending in fetal intrauterine death or miscarriage all had ratios similar to those found for open NTD. For fetuses with ventral wall defects alone all values were ≤0·12, irrespective of blood staining. No overlap was seen between the AChE/BuChE-ratios for fetal ventral wall defects and fetal open NTD, open spina bifida together with ventral wall defects, fetal intrauterine death, or miscarriage. Four amniotic fluid samples with combined false positive elevated AFP and AChE results all had ratios of ≤0·13, fairly similar to the range for ventral wall defects.

Discussion

In this study we have examined AChE/BuChE-ratios in amniotic fluid samples with elevated levels of both AFP and AChE. AChE and BuChE activities were determined by immunoassays specific for each enzyme. In accordance with other studies we have found that, for samples not visibly contaminated with blood, AChE/BuChE-ratios make it possible to distinguish open NTD from fetal ventral wall defects (Goldfine *et al.* 1983; Wald *et al.* 1984). For blood contaminated samples, becoming clear after centrifugation, our results indicate that dif-

Table 1. Summary of distributions of AChE and BuChE and of AChE/BuChE-ratios for anencephaly (An), open spina bifida or encephalocele (OSB), open spina bifida together with ventral wall defect (OSB + VWD), ventral wall defect (VWD), intrauterine fetal death or miscarriage (IUD) and unaffected normal pregnancies, related to the state of blood staining of the sample

	AChE (nkat/l)			BuChE (nkat/l)			AChE/BuChE-ratio			
Diagnosis	Median	25th–75th centile	Range	Median	25th–75th centile	Range	Median	25th–75th centile	Range	*n*
Clear samples										
An	61·40	29·60–111·00	11·20–194·00	116·20	68·42–176·48	20 85– 218·29	0·54	0·36–0·71	0·15–1 74	13
OSB	69·00	43·45– 98·05	9·23–155·00	63·31	45·94– 86·66	21·07– 157·47	1·11	0·80–1·46	0·19–2·86	37
OSB + VWD	541·50	–	106·00,977·00	255·70	–	87·86, 423·54	1·76	–	1·21,2·31	2
VWD	20·50	13·10– 42·70	12·60–129·00	218·29	177·02–641·83	163·99–1705·02	0·08	0·06–0·09	0·06–0·12	7
IUD	50 90	–	26·10,50·90,414·00	107·51	–	97·74,107·51,213·94	0·47	–	0·27,0·47,1·94	3
Unaffected	–	–	–	–	–	–	–	–	–	*n*
Blood stained samples—clear after centrifugation										
An	89·75	59·23–114·00	39·50–220·00	146·61	115·12–211·55	83·51– 335·57	0·52	0·34–0·88	0·19–1·70	24
OSB	67·75	43·80–116 25	14·20–148·00	78 74	48·87–104·36	21·94– 169·42	1·12	0·62–1·83	0·15–1·89	10
OSB + VWD	–	–	32.20	–	–	132·49	–	–	0·24	1
VWD	14·10	–	10·20,14·10,25·60	154·21	–	89·05,154·21,293·22	0·09	–	0·09,0·09,0·11	3
IUD	–	–	62·50	–	–	106·43	–	–	0 59	1
Unaffected	16·10	–	9·08,16·10,28·20	135·75	–	130·32,135·75,219·37	0·12	–	0·07,0 12,0·13	3
Blood stained samples—not clear after centrifugation										
An	147·00	–	47·70,147·00,316·00	175·93	–	120·55,175·93,178·10	0·84	–	0·40,0·84,1·77	3
OSB	–	–	–	–	–	–	–	–	–	–
OSB+VWD	–	–	–	–	–	–	–	–	–	*n*
VWD	–	–	203 00	–	–	5364·84	–	–	0·04	1
IUD	361·10	–	98·20,624·00	162·90	–	155·30,170·50	2·15	–	0·63,3·66	2
Unaffected	–	–	32·70	–	–	402·91	–	–	0·08	1

ferential diagnosis of open NTD and ventral wall defects might be possible using AChE/BuChE-ratios; this is in contrast to Goldfine *et al* (1983). The discrepant result might be due to the technique used or differences in the degree of blood contamination of the samples. For the blood stained samples, that remained discoloured after centrifugation, a separation of open NTD and ventral wall defects might be possible, but the small number of samples analysed in this study makes this result uncertain. Blood contaminated samples with combined false positive AFP and AChE results gave AChE/BuChE-ratios below those seen for open NTD, in accordance with previous reports (Peat & Brock, 1984; Burton, 1986; Kelly *et al.* 1989) In all pregnancies ending in fetal intrauterine death or miscarriage, ratios were within the range found for open NTD. A cut-off value of 0·14 seems useful irrespective of blood staining of the sample.

Analytical repeatability can be critical when results from two analyses are combined. Between-run precision has therefore been determined for both immunoassays separately. For the range of AChE and BuChE activities measured, between-run coefficients of variation of about 5% have been found. Assuming that the two immunoassays vary independently a combined coefficient of variation of about 7% can be calculated; a result that is acceptable.

Our results indicate that for amniotic fluid samples with elevated levels of AFP and AChE the ratio between immunochemically determined AChE and BuChE (AChE/BuChE-ratio) gives valuable information useful for distinguishing open NTD and fetal intrauterine death or miscarriage from ventral wall defects or false positive results due to blood contamination Discrimination between these conditions is not possible on the basis of AFP and AChE results alone. The study has, however, been performed on selected pregnancies and only a few blood stained samples remaining discoloured after centrifugation have been analysed. It is therefore possible, that with the accumulation of more results, an overlap between the diagnostic groups might appear. The procedure we have described is simple to carry out and much more rapid than the previously described method based on densitometry following gel electrophoresis.

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Babies born before arrival at hospital

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Abstract

Objective—To establish the prevalence of babies born before arrival at two local hospitals. To identify women at risk of giving birth before arrival, and the morbidity and mortality associated with such births.
Design—A case control study. Each baby born before arrival and its mother were compared with the next born in the hospital (random control), and one matched for gestation and birthweight, together with their mothers.
Setting—Two maternity units serving East Birmingham and Solihull.
Subjects—All babies (and their mothers) born before arrival at these hospitals from January 1983 to December 1987.
Main Outcome Measures—Perinatal mortality rates, patterns of perinatal morbidity, demographic, social and obstetric features of the mothers.
Results—137 (0·44%) of 31 140 consecutive births were before arrival at hospital (BBA group). The perinatal mortality rate in the BBA group was 58·4/1000 (8 deaths) compared with 10·1/1000 for all inborn babies (relative risk 5·8, 95% confidence interval 2·9–11·4). In the BBA group the mean birthweight of 3008 g was 212 g (95% CI 50–374 g) less than that in the random control group; the mean gestation of 266 days was 10 days less (95% CI 5·9–14·1 days) than in the random control group. Hypothermia was the commonest morbidity. Women delivered before arrival tended to be either multigravid inner city Asians living a long way from the hospital or unmarried unbooked younger white Europeans.
Conclusions—The high perinatal mortality was related to immaturity and low birthweight, rather than to birth before arrival itself. Although groups of mothers at risk of delivery before arrival can be identified more information is needed to establish whether additional antenatal care would be beneficial for these women and their babies

The percentage of births occurring at home in England and Wales has fallen from 3·2% in 1975 to 0·95% in 1987 (Campbell & Macfarlane 1987, Office of Population Censuses and Surveys 1988). Whilst the overall perinatal mortality rate fell from 19·2 to 8·9/1000 during this time, the perinatal mortality rate for home births increased from 18·6 to 21·7/1000 (in 1985) (Campbell & Macfarlane 1987) Campbell *et al* (1984) showed that planned home births had a perinatal mortality rate of 4·1/1000, compared with 67·5/1000 for those who intended to give birth in hospital but did so at home, and 196.6/1000 births booked neither for home nor hospital.

Studies in the 1970s reported on mortality rates, social factors associated with home births (Campbell *et al.* 1984, Murphy *et al.* 1984) and, to a limited extent, on neonatal morbidity (Murphy *et al.* 1984). As the overall mortality and morbidity of babies born in our two maternity units has diminished, the problems presented by

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babies born before arrival (BBA) at hospital have become increasingly apparent.

We studied these babies and their mothers in order to: (i) establish the prevalence of birth before arrival in our local population; (ii) estimate the perinatal mortality rate of babies born before arrival; (iii) identify groups of women at risk of giving birth before arrival; (iv) identify morbidity related to being born before arrival.

The study was approved by the local medical ethical committee.

Subjects and methods

The records of all babies born before arrival in hospital in two adjacent maternity units, Marston Green and Solihull Hospitals, in the 5 years from January 1983 to December 1987, were reviewed. In order to compare outcomes, each of these babies (BBA group) was compared with two controls. One was the next baby born in that same hospital (random control), and the second was the next baby in that hospital matched for weight and gestation (matched control). A match was achieved if a baby had both a birthweight within 200 g *and* a gestation within 14 days of the index case. Fetuses weighing <500 g were excluded from the study. For the one pair of twins in the case group, one random and one matched baby was found for each twin, but only the first random and first matched mother were used to compare maternal characteristics.

For each baby the mother's marital status, age, parity, race and booking status were recorded. The straight line distance from home to hospital was measured from maps. The date, time and place of birth, and mode of transport to hospital were noted. The presence of hypothermia, hypoglycaemia, respiratory distress, infection, birth trauma, jaundice and neurological morbidity in the baby was also recorded.

Marston Green and Solihull Hospitals are 6 miles apart. They serve the districts of Solihull and East Birmingham, as well as adjacent rural areas of Warwickshire. Thus, the mothers came from a wide range of backgrounds. with the most marked contrasts being between the deprived inner city areas of East Birmingham, where 60% of the mothers are Asian, to the affluent areas of Solihull and the surrounding countryside, with only a few non-European families.

Statistical analysis was by Student's *t*-test for differences between means, and by χ^2 and Fisher's exact probability test for differences between proportions, the latter being used for small numbers. Odds ratios and confidence intervals were calculated with standard techniques (Gardner & Altman 1986).

Results

Of the 31 140 babies born to women admitted to the two maternity units in the 5 year study period 137 (0·44%) were born before arrival in hospital.

A total of 136 women gave birth before arrival, there was one set of twins. Table 1 shows that the mothers who were delivered before arrival were significantly more likely to be older and of higher parity, to be Asian, to be unbooked and to live further from the hospitals than the mothers in either of the control groups. The main difference in age distribution occurred at the extremes, with the study group having fewer mothers under 20 years, and more over 35. The modal maternal age was 21–25 years in all three groups. This was reflected in the parity distribution with fewer primigravid women being delivered before arrival, and with an excess of high parity ($\geq$3) mothers in that group.

There was no relation between marital status and giving birth before arrival. However, all the Asian mothers were married, and, if they are excluded from the analysis, 35 of remaining 82 mothers were single or divorced, compared with 29 of 113 random and 32 of 112 matched control mothers ($\chi^2 = 7.0$, df = 2, $P<0.05$).

Fifteen (19%) of the European mothers were primiparous, compared to only one (2%) of the Asians (P = 0·0015, Fisher's exact test, odds ratio = 12·8, 95% confidence interval (CI) = 1·7–94·0). Twelve (16%) of the Europeans were under 20 years of age, but only one Asian (P = 0·0075, Fisher's exact test, odds ratio 9·8, 95% CI 1·3–73·0).

Four of the 120 multiparous mothers who gave birth before arrival in the study period had done so in a previous pregnancy: none of the mothers in the control groups had done so.

Compared with the two control groups, the proportion of babies born before arrival rose significantly the further the mother's home was from the hospitals.

Separate analysis of the random and matched control groups showed that there were no significant differences between them for any of the maternal characteristics analysed in Table 1.

Seventeen (13%) women in the BBA group

Table 1. Characteristics of women who gave birth before arrival in hospital (BBA) and two control groups

Maternal variables	BBA	Random	Matched	Significance
Age (years)				
<21	19	26	24	
21–25	54	48	47	
26–30	22	33	45	df = 8, χ^2 = 18.1, P = 0·02
31–35	27	20	16	
>35	14	9	4	
Parity				
0	16	46	45	
1	32	42	50	
2	32	23	22	df = 8, χ^2 = 48·3, $P \ll 0{\cdot}001$
3	29	9	8	
≥4	27	16	11	
Marital status				
Married	101	107	104	
Single	29	25	30	Not significant (but see text)
Divorced	6	4	2	
Race				
European	77	108	106	
Asian	54	23	24	df = 4, χ^2 = 24·8, $P \ll 0{\cdot}001$
Other	5	5	6	
Booking status				
Unbooked	17	1		$P \ll 0{\cdot}001$
Booked	119	271		Fisher's exact test
Distance of home from hospital (km)*				
<2	4	29	26	
2–7	88	83	78	df 4, χ^2 = 27·2, $P \ll 0{\cdot}001$
>7	42	21	27	

* Uncertain for nine women, data excluded

were unbooked, compared with only one of the 272 control mothers ($P \ll 0{\cdot}001$). Table 2 shows that unbooked women were more likely to be under 25 years (81%), unmarried (71%), primigravid (53%) and European (82%) than the booked mothers giving birth before arrival. They did not, however, live further from the hospitals. Four of the 11 unmarried women had concealed their pregnancies: three were primigravid Europeans under 20 years of age, the fourth was mentally handicapped. Three of these four babies were the only ones in the study offered for adoption immediately after birth

It proved impossible to estimate accurately the length of labour in women who gave birth before arrival. For 12 of these women the midwives felt unable to estimate the blood loss. Three of the remaining 124 women had a postpartum haemorrhage of >500ml. Of the 272 women in the control groups 33 (12·1%) were delivered by caesarean section, of the other 239 who gave birth vaginally only two had a postpartum haemorrhage of >500 ml. Two women who were delivered before arrival had a third degree tear, compared with one in the control groups. One woman delivered before arrival had a manual removal of the placenta, compared with four women in the control groups There are no significant differences between the groups for any of these figures.

Place of birth

Of the 137 babies born before arrival in hospital 103 (75%) were born at the mother's home, 24 (18%) en route to the hospital in an ambulance

Table 2. Comparison of booked and unbooked women who gave birth before arrival

Maternal variables	Booked	Unbooked	Significance
Age (years)			
<21	12	7	
21–25	48	6	
26–30	20	2	df = 4, χ^2 = 13 4, P <0·01
31–35	25	2	
>35	14	0	
Parity			
0	7	9	
1	28	4	
2	30	2	df = 4, χ^2 = 33·2, P≪0·001
3	28	1	
≥4	26	1	
Marital status			
Married	96	5	
Single	18	11	df = 2, χ^2 = 22·5. P≪0·001
Divorced	5	1	
Race			
European	63	14	
Asian	51	3	European *vs* Asian+others
Other	5	0	P = 0·019, Fisher's exact test
Distance of home from hospital (km)*			
<2	4	0	
2–7	73	15	NS
>7	40	2	

* Uncertain for nine women, data excluded. NS = Not significant.

or a car, nine (7%) in the hospital grounds or car park and one in a public toilet.

Birthweights and gestation

Table 3 shows that the mean (SD) birthweight of 3008 (725) g in the BBA-group was significantly lower than that of 3220 (638) g in the next born babies (random control group)' (P<0·02, 95% CI of difference 50–374 g). Thirty two (23%) of the babies born before arrival were preterm (<37 completed weeks gestation), significantly more than the 16 (12%) in the random control group (χ^2 5·7, P<0·02, odds ratio 2, 95% CI 1·2–3·5); the mean gestation of 266 (SD 22·5) days was significantly shorter than that of 276 (9·3) days in the random control group (P<0·001, 95% CI of difference 5·9–14·1 days). There were no significant differences between the BBA-group and the matched control group. Part of the difference in mean birthweights and gestations between the groups could have been attributed to the higher proportion of Asian babies in the BBA group. Table 3 shows that the mean birthweight of European babies born before arrival was significantly higher than that of Asian babies in that group, and there was a trend for their gestation to be longer. These calculations exclude 5, 6 and 6 babies from other ethnic groups in the BBA, random and matched groups respectively.

Morbidity

There were four stillbirths in the BBA-group, one in the random control group, and three in the matched control group. Thus, morbidity was compared between 133, 136 and 134 liveborn babies respectively in three groups.

Hypothermia, defined as a rectal temperature of ≤35.0°C, was the most common problem in the 133 babies born alive before arrival. Table 4 shows that 38 (31%) of the 124 who had had their temperature recorded were hypothermic, com-

Table 3. Birthweight and gestation of babies born before arrival (BBA) and two control groups

	BBA	Random	Matched	Significance (BBA *vs* random)
Total number	137	137	137	
Birthweight (g)	3008 (725)	3220 (638)	3016 (714)	$t = 2\cdot57$, $P<0\cdot02$
<2500 g				
n (%)	26 (19·0)	15 (10·9)	26 (19·0)	NS
Gestation (days)	266 (22·5)	276 (9·3)	268 (20·9)	$P<0\cdot001$
<37 weeks				
n (%)	32 (23·4)	16 (11·7)	26 (19·0)	$\chi^2 = 5\cdot7$, $P<0\cdot02$
No of Europeans	78	108	107	
No. Asians	54	23	24	
Birthweight (g)				
European	3124 (810)	3294 (557)	3074 (734)	NS
Asian	2848 (601)	3035 (782)	2924 (640)	NS
European *vs* Asian	$P<0\cdot05$	NS	NS	
Gestation (days)				
European	270 (26.5)	278 (15)	269 (19·9)	$P<0\cdot02$
Asian	264 (16·4)	267 (11·3)	270 (12·9)	NS
European *vs* Asian	NS	$P<0\cdot001$	NS	

Results are mean (SD) or *n*(%) values as appropriate.
NS = Not significant.

pared with only five (2%) of 214 control babies ($P \ll 0\cdot001$, odds ratio 13.2, 95% CI 5·4–33·3). In the BBA-group, 16 (73%) of the 22 babies weighing <2500 g were hypothermic, compared with 22 (23%) of 97 heavier babies (χ^2 18·4, $P \ll 0\cdot001$, odds ratio 3.2, 95% CI 2·0–5·0). The relation with gestational age was not quite significant, for 14 (48%) of 29 preterm and 24 (27%) of 90 term babies were hypothermic ($\chi^2 = 3\cdot77$, $P = 0\cdot052$). The development of hypothermia was not related to place of birth (i.e., home, ambulance or hospital grounds), distance of the maternal home from the hospitals, time of year or time of day.

Thirty six (27%) of the 133 babies born alive before arrival were admitted to the neonatal units, compared with 10 (7·4%) of 136 random liveborn controls, and 20 (14·9%) of 134 liveborn matched controls (χ^2 19.4, df = 2, $P<<0\cdot001$). A significant difference persisted even if only the BBA and matched control groups were compared (χ^2 5·23, $P<0\cdot05$, odds ratio 1·8, 95% CI 1·1–3·0). This difference was accounted for entirely by 16 babies born before arrival being admitted primarily for treatment of hypothermia. The other most common reason for admission to a neonatal unit was immaturity and/or low birth weight, with 14, 7 and 10 babies

Table 4. Morbidity in liveborn babies born before arrival (BBA) and two control groups

	BBA	Random	Matched	Significance
Number liveborn	133	136	134	
Temperature known	124	106	108	$\chi^2 = 13\cdot3$, $P<0\cdot002$
Hypothermic (≤35°C)	38	5		$P \ll 0\cdot001$: BBA *vs* both control groups, Fisher's exact test
Admission to NNU	36	10	20	$\chi^2 = 19\cdot4$, $P \ll 0\cdot001$

NNU = neonatal unit

in the BBA, random and matched control groups, respectively, being admitted in that category.

There were no significant differences between the groups for the prevalence of post-asphyxial encephalopathy (1 to 2 babies in each group, but none with fits or coma), jaundice, infection rates or respiratory distress. None of the babies who were followed up because of perinatal problems was handicapped when examined at their last appointment.

Mortality

The deaths in babies born before arrival fell into three groups. Four of the eight were extremely immature with gestations ≤25 weeks. This group included extremely immature twins of 25 weeks gestation: the first weighed 500 g and was admitted with a core temperature of 30°C and died at 90 min, the second was a fresh stillbirth into a toilet. Two other babies, weighing 500 g and 670 g at 24–25 weeks gestation died within hours of birth. Three were macerated stillbirths at 36–40 weeks gestation. One woman with hypertension and suspected severe intrauterine growth retardation repeatedly refused admission to hospital only to give birth to a macerated stillbirth weighing 1200 g at 36 weeks gestation. Two other macerated stillbirths weighed 1900 g at 37 weeks and 2700 g at 40 weeks gestation. One term baby with severe arthrogryposis and suspected pulmonary hypoplasia survived only 2 days. Similarly in the matched control group three babies were born at ≤26 weeks gestation, they weighed between 625 g and 800 g, and all died within 36 h of birth; there were three macerated stillbirths (at 28, 38 and 39 weeks); and one other neonatal death from severe respiratory distress in a baby of 1050 g born at 34 weeks gestation. The four deaths in the random control group were one at 28 weeks from respiratory distress syndrome, a macerated stillbirth at 28 weeks, a pulmonary haemorrhage at 34 weeks, and pulmonary hypoplasia at 36 weeks.

Eight of the 137 babies born before arrival died, a significantly higher proportion than the 314 who died out of 31 003 inborn babies (χ^2 26·5, df = 1, $P \ll 0·001$). The perinatal mortality rate for babies born before arrival was 58·4/1000, and for all inborn babies was 10·1/1000. Thus, babies born before arrival were 5·8 times (95% CI 2·9–11.4) more likely to die. However, when compared with the group matched for weight and gestation, which had a perinatal mortality rate of 51·1/1000 (7/137) and the random group (which had an unexpectedly high number of deaths) with a perinatal mortality rate of 29·2/1000 (4/137), significant differences were no longer found. This was true even when two babies with lethal congenital abnormalities (one born before arrival with severe arthrogryposis and one random control with pulmonary hypoplasia) were excluded. By chance, the random control group had a perinatal mortality rate 2·9 times higher than the remaining 30 886 inborn babies, of whom 310 died. This difference is just significant with 95% CI of the odds ratio being 1.1–7.7.

Mortality within each of the three groups was examined with relation to gestational age, birthweight, and parity (Table 5). In the BBA and matched control group there were statistically significant differences in perinatal mortality between primiparous and multiparous mothers, between preterm and term babies and between low birthweight babies and babies weighing more than 2500 g These differences did not quite reach significance in the random group. No significant differences in perinatal mortality rates were found between the three groups when examined by any of these subdivisions of parity, preterm birth and birthweight.

For those babies born before arrival, there were no significant differences in perinatal mortality rates between the 82 European (61·7/1000) and the 55 Asian babies (54·5/1000). All four very preterm babies born before arrival were European, as were the three in the matched group. The perinatal mortality rate of 103/1000 (3 deaths) for the 29 unmarried women delivered before arrival was not significantly higher than that of 47/1000 (5 deaths) in married women; nor was that of 118/1000 (2 deaths) in the 17 unbooked women compared with 50/1000 (6 deaths) in those who had booked. The perinatal mortality rate was not related to time of day of the birth, time of year, nor to the distance of the mother's home from the hospital.

Discussion

It must be pointed out that this study was restricted to babies who were born outside the hospital and subsequently admitted. When the baby of a hospital booked woman was born at home and was not admitted to hospital we have no infor-

Table 5. Perinatal mortality for babies born before arrival (BBA) compared with random and matched control groups, by gestational age, birthweight and maternal parity

	BBA	Random	Matched
Total	8/137 (58)*	4/137 (29)	7/137 (51)
Gestation			
Preterm	5/32 (143)	2/16 (125)	5/26 (192)
Term	3/105 (29)	2/121 (17)	2/111 (18)
Preterm *vs* term	$P = 0{\cdot}017$	$P = 0{\cdot}067$	$P = 0{\cdot}0029$
Birthweight (g)			
<1500	7/7 (1000)	2/4 (500)	7/8 (875)
1500–2499	0/19	0/11	0/18
≥2500	1/111 (9)	2/122 (16)	0/111
<2500 *vs* ≥2500	$P = 0{\cdot}00003$	$P = 0{\cdot}059$	$P = 0{\cdot}000004$
Parity			
Primiparous	4/16 (250)	3/46 (65)	5/45 (111)
Multiparous	4/120 (33)	1/90 (11)	2/91 (22)
Primiparous *vs* multiparous	$P = 0{\cdot}007$	$P = 0{\cdot}11$	$P = 0{\cdot}04$

* Figures in brackets indicate perinatal mortality rate/1000·

Significance testing used Fisher's exact probability test, there were no significant differences between the three groups

mation and data are particularly difficult to collect.

In this study, the perinatal mortality rate of babies born before arrival (58·4/1000) was significantly higher than that of the 31 003 inborn babies (10·1/1000) for the 5-year study-period. However, the group matched for birthweight and gestation had a virtually identical rate (51·1/1000) Babies born before arrival had a significantly lower mean birthweight and significantly shorter mean gestation than those in the random (next born) control group. A significantly higher proportion were preterm. When perinatal mortality rates in the BBA and matched groups were examined by birthweight or gestation bands (Table 5), there were no significant differences between the groups in any weight or age band Comparison of perinatal mortality rates between preterm and term, and between low birthweight babies and those with weights ≥2500 g in these two groups showed the expected increase in perinatal mortality with diminishing birthweight and gestation. Therefore birth before arrival did not in itself significantly prejudice the chances of survival, rather the higher perinatal mortality in this group was secondary to the greater prevalence of immaturity and/or low birthweight.

The principal morbidity related to birth before arrival was hypothermia. Of babies whose temperature was recorded, only 5 (2·3%) of the 214 hospital born babies dropped to ≤35°C, compared with 38 (30·6%) of the babies born before arrival. Within the BBA group, hypothermia was significantly more frequent in low birthweight babies; no such relation was found in the matched control group. Thus, unlike the increased mortality, the increased occurrence of hypothermia was secondary to birth outside the hospital.

Admission to the neonatal units for a variety of reasons, including hypothermia and suspected hypoglycaemia, was significantly more frequent in babies born before arrival. Again this was not just a phenomenon of immaturity or low birthweight, as the difference persisted even when the comparison was made only between the BBA and matched control groups.

Analysis of a number of maternal characteristics revealed that women delivered before arrival were significantly more likely to be older and of high parity, to be Asian, to live further from the hospitals and to be unbooked. Within the population studied, however, there were two distinct subgroups One comprised older, booked multigravid Asian women who lived in inner East Birmingham some 8–11 km from the hospitals; the other was of unmarried unbooked

Europeans with a high proportion of primiparous women, some of whom concealed their pregnancies. Not all of the women giving birth before arrival fell into these two categories, but they comprised two large and important groups whose health-care needs were not met. We suggest that these Asian women gave birth before arrival because they had short labours typical of multigravidae, did not have a car to transport them the considerable distance to hospital, and perhaps in some cases, had language difficulties which reduced their ability to avail themselves of midwife, doctor and ambulance services The unbooked European women tended to be younger, unsupported, and of lower parity, and, perhaps for different reasons, they also tended not to avail themselves of full antenatal care. This latter group of women delivered before arrival at hospital included the four very preterm babies who died.

The morbidity of the baby born before arrival is not trivial, but with proper nursing and medical protocol, the common problems of hypothermia and potential hypoglycaemia should be anticipated and prevented, or treated promptly alongside the mothers in transitional care wards. Improvements in neonatal care will contribute to a reduction in mortality in the very preterm low birthweight babies. Nevertheless, birth before arrival at hospital remains a significant problem affecting 0·4% of deliveries, but contributing 2·5% of all perinatal deaths. Distinct and different groups of women are at risk of such deliveries, and the provision of appropriate antenatal care to them can be difficult. To reduce the excess perinatal mortality and morbidity associated with this event, special consideration should be given to inner city Asian women and young, single, unsupported European girls. We are, however, unaware of any studies in the United Kingdom which have reported a reduction in births before arrival as a result of increased antenatal support. The problem is likely to continue.

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Smoking during pregnancy: a significant cause of neonatal thyroid enlargement

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Summary. The influence of maternal smoking during pregnancy on the function and the echographic volume of the neonatal thyroid gland was examined in an area of borderline iodine intake (median maternal urinary iodine: 315 range 79–1558 nmol/l). There was a positive correlation ($P<0.001$) between cord serum thiocyanate (SCN) concentrations used as an index of maternal smoking and the maternal smoking habits. The thyroid volume/birthweight ratio increased significantly as a function of SCN values ($P<0.005$): this increase was secondary to a decrease in birthweight as well as to an increase in thyroid volume. There was also a positive correlation between cord serum thyroglobulin (Tg) and SCN levels ($P = 0.001$). Serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) values remained within the normal range for age in all newborn infants and were not significantly correlated with SCN values. These results show that smoking during pregnancy in areas with borderline iodine intake may be a significant cause of thyroid enlargement in the newborn.

Tobacco smoke contains many different compounds (Nash & Persaud 1988); one of the most important, hydrogen cyanide, is detoxified into thiocyanate (SCN), a goitrogenic substance. The role of SCN in the aetiology of endemic goitre has been clearly demonstrated in the presence of iodine deficiency (Lagasse *et al.* 1982).

The biological half-life of SCN is 4–14 days. It readily crosses the placenta, and maternal smoking results in elevated concentrations of SCN in both mother and fetus. Determination of the concentrations of SCN in cord serum is therefore currently regarded as a reliable index of maternal smoking habits (Jensen & Foss 1981). Previous reports on the influence of maternal smoking on neonatal thyroid function provided conflicting results: Ericsson *et al.* (1987) reported that babies born to smoking mothers had elevated serum concentrations of thyroglobulin (Tg) in cord blood, without significant changes in serum thyroid-stimulating hormone (TSH) values, whereas Meberg & Marstein (1986) reported a moderate decrease in TSH, suggesting a moderate hyperfunction of the thyroid gland; the cause remained unclear. The present work aimed to investigate further whether SCN could be responsible for changes in thyroid size and impairment of thyroid function in infants born to smoking mothers. The study was conducted in Brussels, where the average daily urinary excretion of iodine in adults is borderline, ranging from 50 to 75 μg (390 to 590 nmol) (Delange *et al.* 1986).

Subjects and methods

The study included 82 randomly selected mothers

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and their full term newborn infants (42 males and 40 females) born in our maternity ward during a six months period. There was no known history of maternal thyroid disease or iodine contamination. Median (range) values were 40 (37–42) weeks for gestational age, 3430 (2400–4400) g for birthweight and 9 (3–10) and 10 (6–10) for Apgar scores at 1 and 5 min respectively. Approval for this study was obtained from the local ethics committee and all parents gave informed consent.

SCN and maternal smoking habits

SCN concentration was measured in cord serum in all 82 subjects, using the method of Michajlovskij & Langer (1958). A SCN value <35 μmol/l was considered as a control value (Delange *et al.* 1982). Maternal smoking during pregnancy was assessed from their history: <3 cigarettes/day (non or light smokers), 3–15 cigarettes/day (moderate smokers) and >15 cigarettes/day (heavy smokers).

Neonatal thyroid function and volume

The values of TSH, free thyroxine (FT4) and Tg were determined in cord serum, and neonatal thyroid volume was determined by ultrasonography between the first and third day of life. Urinary iodine was measured on one casual urine sample obtained from the mother between the first and third day postpartum and was used as an index of iodine nutrition. TSH and FT4 were measured with kits from Amersham International, and Tg was measured with a conventional double antibody radioimmunoassay.

Thyroid ultrasonography used a high frequency 7·5 Mhz linear array transducer (Toshiba Sonolayer V-SSA-100A) as described previously by Chanoine *et al.* (1990). Parasagittal and transverse scans were done at the anatomical site of the thyroid gland with hyperextension of the neck allowing the determination of depth, length and width of each lobe; the lobes were assimilated to ovoids and their volume was estimated by the formula: V (volume of one lobe) = π/6 × depth × length × width. The total thyroid volume was obtained by summing up the volume of both lobes. The infant was fed before the examination so that no sedation was required. Maternal urinary iodine was assessed with a fully automated Tecnicon Auto-Analyzer using the Sandell-Kolthoff reaction (Sandell & Kolthoff 1937).

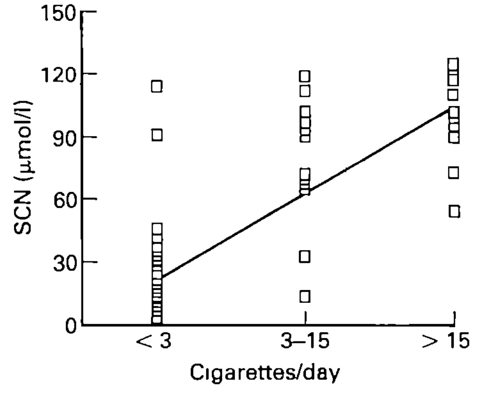

Fig. 1. Relation between cord serum thiocyanate (SCN) concentrations and maternal smoking habits ($n = 82$, $y = -19{\cdot}0 + 41{\cdot}1x$; $r = 0{\cdot}81$; $P<0{\cdot}001$)

Statistics

All data are presented as medians (range). The correlation coefficient (r) and the linear regression were used to express the relation between the different biological, clinical or echographic data. A P value $<0{\cdot}05$ was considered significant.

Results

SCN and maternal smoking habits

There was a positive correlation between cord SCN and maternal smoking habits (Fig. 1). The median SCN value was 17·2 (3·4–113·5) μmol/l in the 58 (71%) mothers who smoked fewer than three cigarettes per day, and 99·8 (53.3–123·8) μmol/l in the 12 (15%) who smoked more than 15 cigarettes per day.

Neonatal thyroid function and volume

Cord serum TSH (5·6, range 1·6–24·6 mU/l; $n = 82$) and FT4 (13·8, range 9·4–29·6 pmol/l; $n = 82$)

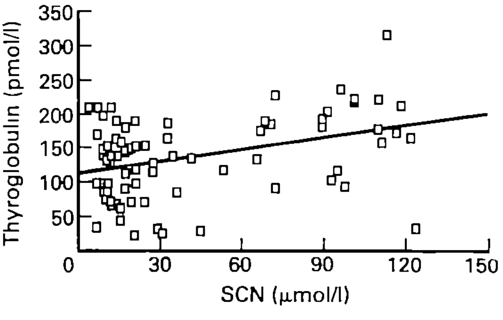

Fig. 2. Relation between cord serum thiocyanate (SCN) and thyroglobulin (Tg) concentrations ($n = 82$, $y = 112{\cdot}52 + 0{\cdot}57x$; $r = 0{\cdot}37$, $P = 0{\cdot}001$)

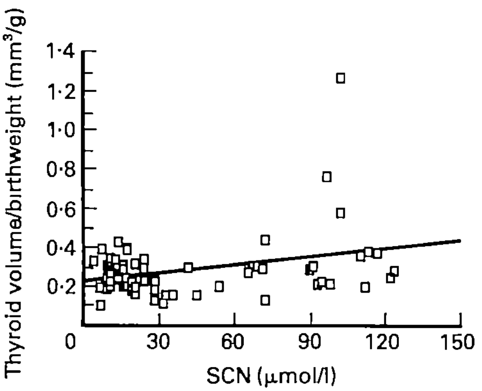

Fig. 3. Relation between cord serum thiocyanate (SCN) concentrations and neonatal thyroid volume corrected for birthweight ($n = 69, y = 0{\cdot}226 + 0{\cdot}001x$; $r = 0{\cdot}34$; $P < 0{\cdot}005$)

values remained within the normal range for age in all infants and were not significantly correlated with SCN values. Cord serum Tg concentrations were 86 (15–140) pmol/l ($n = 53$) for SCN values < 35 μmol/l, a normal range for Brussels standards. As shown in Fig. 2, there was a positive correlation between Tg and SCN.

Neonatal thyroid volume was 868 (313–1760) mm³ ($n = 46$) for SCN values < 35 μmol/l, a normal value for age in Brussels (Chanoine *et al.* 1991). The volume tended to increase with SCN, but the correlation was of borderline significance ($n = 69, r = 0{\cdot}22; P = 0{\cdot}067$). When corrected for birthweight which significantly decreased with the increase in SCN ($n = 82$; $r = 0{\cdot}41$; $P < 0{\cdot}001$; Weight (g) = 3617·00–5·23 SCN (μmol/l)), the relative increase of thyroid volume as a function of SCN was statistically significant (Fig. 3). In the 82 mothers studied, median urinary iodine was 315 (79–1558) nmol/l, a normal observation for Brussels (Delange *et al.* 1986), indicating borderline iodine intake. There was no significant correlation between urinary iodine and thyroid volume or between urinary iodine and thiocyanate.

Discussion

Tobacco smoke contains between 2000 and 4000 different compounds that all seem to affect the smoker to some degree. among the many toxins identified that reach the blood stream, CO, nicotine and hydrogen cyanide form the highest concentrations (Nash & Persaud 1988).

The hydrogen cyanide contained in tobacco smoke enters the blood circulation and is detoxified into SCN in the presence of sulphur containing amino acids. In developed countries, this is definitely the main source of SCN, but it may also be derived from foods (mainly brassicas, cassava and almonds), especially in developing countries (Lagasse *et al.* 1982). Assuming that smoking habits were reported accurately by the mothers, this could explain why a few women smoking fewer than three cigarettes per day had elevated SCN levels (Fig. 1), and why the correlation between smoking habits and SCN values was relatively weak. The latter observation is in complete agreement with the classical specificity and sensitivity reported for serum SCN used as an indicator of smoking (Kornitzer *et al.* 1983).

The present work shows that markedly elevated concentrations of SCN in cord serum, induced mostly by maternal smoking, are associated with decreased birthweight and increased neonatal thyroid volume, resulting in a significant increase in the thyroid volume/birthweight ratio There was also an increase in cord Tg concentrations, without any significant impairment in the level of circulating FT4 and TSH.

Maternal smoking has long been associated with impaired fetal development. Reduced birthweight, also evident from our data, is probably the best documented effect of maternal smoking. The vasoconstrictive effect of nicotine on utero-placental circulation and the elevated carboxyhaemoglobin levels are regarded as the main aetiological factors for the lower birthweight (Mochizuki *et al.* 1984). We recently showed that the volume of the thyroid gland estimated by echography in healthy newborn infants was positively correlated with birthweight (Volume (mm³) = 130·0 + 0·2 Weight (g); $r = 0{\cdot}27$, $P = 0{\cdot}012$) (Chanoine *et al.* 1991). In the present study, thyroid volumes tend to be higher when birthweight is lower. When corrected for birthweight, the relative increase in thyroid volume as a function of SCN, expressed in mm³/g birthweight, is highly significant (Fig. 3). This reflects the adverse effects of maternal smoking on fetal growth as well as on the thyroid gland, and stresses the importance of taking into account the patient's own characteristics when defining the notion of goitre. Indeed, the most widely adopted definition of a goitre is a 'thyroid whose lateral lobes have a volume greater than the terminal phalanges of the thumb of the person being examined' (Delange *et al.* 1986).

The role of SCN as cogoitrogen has been well demonstrated in endemic goitre areas in Central

Africa. In the presence of iodine deficiency, a permissive condition, SCN overload increases iodine excretion in the urine and inhibits iodine uptake by the thyroid gland, decreasing even further the already low iodination level of Tg (Bourdoux *et al.* 1980): increase in serum Tg secretion and thyroid hypertrophy are regarded as the precocious signs of thyroid insufficiency, when TSH and thyroid hormones levels are still in the euthyroid range (Sava *et al.* 1986).

In Brussels, although maternal iodine intake is borderline (Delange *et al.* 1986), neonatal goitre is a rare finding. Our data support the hypothesis that the aggravation of iodine deficiency by elevated SCN concentrations that are as large as these reported in cord serum in endemic areas in Africa (Lagasse *et al.* 1982) is the most important mechanism involved in the antithyroid action of maternal smoking. An additional line of evidence results from the hypersensitivity of the fetoplacental unit to the antithyroid action of SCN; SCN interferes with the trapping of iodide not only by the fetal thyroid gland but also by the placenta (Logothetopoulos & Scott 1955). Because of the small intrathyroid iodide pool, these two factors act in synergy to reduce the iodine supply from the mother to the fetal thyroid, and therefore reduce the build-up of iodine stores within the gland, which takes place mainly during late fetal and early postnatal life.

In conclusion, smoking during pregnancy in areas with borderline iodine intake may be responsible not only for elevated serum levels of thyroglobulin but also for neonatal thyroid enlargement. This work provides further evidence for the pernicious effects of maternal smoking on child health.

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Distal urethral electrical conductance (DUEC)—a preliminary assessment of its role as a quick screening test for incontinent women

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Summary. Measurement of distal urethral electrical conductance (DUEC) has been used to detect the movement of urine along the distal urethra. DUEC was used as a screening test in 100 women attending the urodynamic clinic with incontinence and in the 33 women who voided over 250 ml, the findings correlated well with subsequent urodynamic diagnosis of urethral sphincter incompetence and detrusor instability.

Movement of urine along the urethra has been measured by registering a change in conductivity reading (Plevnik *et al.* 1985). This relies on urothelium and urine having a different electrical impedance. The distal urethral electrical conductance (DUEC) catheter is a 2 cm long 7FG silastic catheter with two gold plated brass electrodes mounted near the tip. The electrodes are 1 mm wide and 1 mm apart and are connected to a meter reading in μA. A constant, non-stimulatory, sinusoidal voltage with an amplitude of 20 mV peak to peak and a frequency of 50 kHz is applied across them and the current measured is proportional to the conductance of whatever is between the electrodes. Urine with its high salt content gives a high reading while urothelium and absence of urine gives a low reading. The meter can also be connected to a recorder to give a permanent graphic record of the conductivity change. As the catheter is only placed in the distal urethra, full catheterization is not performed. It is held in place by a silastic cuff which sits between the labia.

Three patterns of conductivity change have been described (illustrated in Fig. 1) and these correlate well with the urodynamic diagnosis (Holmes *et al.* 1985 and Peattie *et al.* 1988). A type I pattern comprises spikes of conductivity of >8 μA lasting 2 s (Fig. 1, top). The type II pattern rises in conductivity during raised intra-abdominal pressure with superimposed spikes >8 μA (Fig. 1, middle). Type III changes are increases in conductivity >8 μA lasting >3 s (Fig. 1, bottom). Type I and II patterns have been shown to correlate with a diagnosis of stress incontinence and type III patterns correlate with a cystometric diagnosis of detrusor instability. These patterns have been described during cystometry with the patient standing at full bladder capacity (Peattie *et al.* 1988).

We decided to investigate whether this test could be used in the outpatient clinic as a quick and simple screen for patients complaining of incontinence

Subjects and methods

The study included 100 consecutive new patients with incontinence attending the urodynamic clinic. The patients were asked to attend with a comfortably full bladder and not to void until instructed. On arrival a brief history of the symptoms of stress incontinence, urgency, urge incontinence and urinary frequency was taken. The DUEC catheter was inserted into the distal urethra with the patient in a standing position. The patient was asked to cough once, then six times in a row and then to wash her hands under

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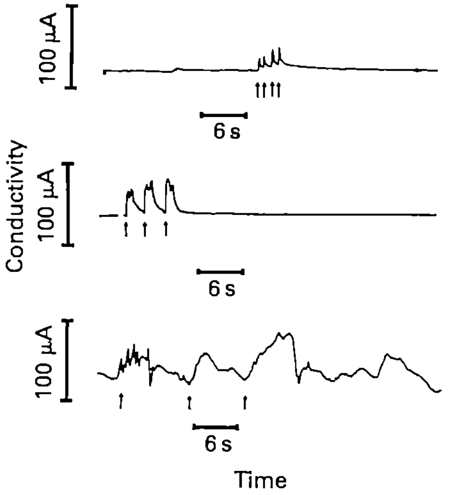

Fig. 1. Patterns of conductivity change measured by distal uretheral electrical conductance. The arrows mark the point at which the patient is asked to cough. Top = type I conductivity pattern; middle = type II conductivity pattern; bottom = type III conductivity pattern (this pattern is provoked by hand washing)

running water The procedure takes about 2 min to perform. Any changes in conductivity were interpreted. A diagnosis of stress incontinence was made if pattern I or II occurred, a diagnosis of detrusor instability was made if pattern III was observed and the diagnosis of a mixed picture was made in the presence of pattern III associated with pattern I and/or pattern II. If no leakage occurred the DUEC diagnosis was recorded as no abnormality detected. This diagnosis was then kept separate from the patient's notes. After performing the DUEC, each patient was asked to void and the peak flow rate and volume voided were recorded using a Lectromed flow monitor 4981.

The patients underwent urodynamic studies comprising either twin channel subtracted cystometry or videocystourethrography and uroflowmetry. The tracing was then interpreted by other members of the urodynamic team. Only after diagnosis was made, were the DUEC and cystometry findings compared.

Results

Their mean age of the 100 patients was 49·9 years (range 19–85 years). Mean parity was 2·3 (range 0–7) and mean weight was 72·9 kg (range 47·5–116 kg). Twenty three patients had undergone previous continence or prolapse surgery.

Table 1 gives the result of DUEC diagnosis compared with the diagnosis on urodynamic studies in all 100 women. DUEC correlated with cystometry in only 55 patients and gave an incorrect diagnosis in 45 patients. Of the incorrect diagnoses, 11 were incorrect positive diagnoses and 34 were false negative results (i.e., a normal result although a later abnormality was detected by cystometry).

However, if the results are analysed for the

Table 1. Correlation between distal urethral electrical conductance (DUEC) and cystometrogram (CMG) diagnoses in 100 incontinent women

	CMG diagnosis			
DUEC diagnosis	GSI	DI	Mixed	No abnormality
All women ($n = 100$)				
GSI	36	5	2	0
DI	2	3	0	0
Mixed	2	0	1	0
No leak	14	13	7	15
Women with voided volume >250 ml ($n = 33$)				
GSI	20	0	0	0
DI	0	3	0	0
Mixed	0	0	1	0
No leak	2	0	0	7
Women with mixed symptoms and voided volume >250 ml ($n = 23$)				
GSI	14	0	0	0
DI	0	2	0	0
Mixed	1	0	1	0
No leak	1	0	0	4

DI = detrusor instability; GSI = genuine stress incontinence subgroup of 33 women who voided over 250 ml of urine, the DUEC gave the correct diagnoses in 31 (94%) and a false negative result in only two (6%) and there were no incorrect diagnoses or false positive results.

Of the 33 women who voided >250ml, 23 had mixed symptoms of urge and stress incontinence and in this subgroup the DUEC and cystometragram diagnoses correlated in 21 patients (91%). One patient had a false negative result with DUEC when cystometry revealed genuine stress incontinence. In one patient the DUEC diagnosis was incorrect as it showed detrusor instability and stress incontinence although cystometry only revealed genuine stress incontinence.

We also looked at the women with symptoms purely of stress incontinence and no complaints of urge incontinence or urinary frequency. This group only comprised 14 women and when restricted to those with more than 250 ml voided volume comprised only six. In this small group, DUEC was correct in five and negative in the sixth. As these patients would be eligible for surgery, it is important to note there were no incorrect diagnoses or missed diagnoses of detrusor instability.

Discussion

There is often a discrepancy between clinical history and urodynamic findings. Jarvis *et al.* (1980) found the clinical diagnosis to be accurate in only 65% of patients. Cystometry is therefore necessary to enable the correct treatment to be given. However, in some areas urodynamic studies are not available or there may be lengthy waiting lists. In addition, cystometry is associated with a risk of urinary tract infection (Walter & Vjelsgaard 1978). DUEC has been shown to correlate well with cystometry in a laboratory situation. We found it to be a quick investigation and feel it may be a useful screening test in the above situations. If the DUEC is positive, uroflowmetry is performed to exclude voiding difficulties after which the treatment can be determined. If the DUEC is negative and the voided volume is less than 250 ml, the test is repeated with a full bladder.

The critical factor in determining the effectiveness of the test is the volume of urine in the patient's bladder. Although all patients were asked to attend with a full bladder, only 46 had more than 200 ml in their bladders and only 33 had more than 250 ml. Overall results show the correct diagnosis in only 55% of patients, but if the patient had more than 250 ml in her bladder the correct diagnosis was made in 94%. In order to improve the percentage of patients attending with full bladders, more emphasis could be placed on this in the appointment letter and greater efforts made to prevent the patient emptying her bladder until the test has been performed.

DUEC may be particularly useful in the diagnosis of stress incontinence. Cystometrically proven detrusor instability was not found in any patient with a bladder volume of over 250 ml in whom a diagnosis of stress incontinence was made with DUEC. This is clinically very relevant as these patients would be treated surgically and, if undetected, detrusor instability could be aggravated.

Two patients with voided volumes of less than 250 ml had a type III pattern on DUEC, suggesting detrusor instability; both of them had stable cystometry, but the type III pattern persisted when DUEC was repeated with a full bladder. These patients may have urethral instability. Currently they have been treated as if they had stress incontinence, although it is not yet certain if this is the correct management and further work may elucidate this.

Another advantage of DUEC is the cost. The DUEC apparatus costs approximately £500 and each catheter approximately £40, the apparatus can be used with the Lectromed flowmeter as a chart recorder which costs approximately £1500. The catheters last 3 months with careful use and there is no requirement for catheter packs or sterile saline. The catheter is sterilized between patients by soaking in glutaraldehyde (Cidex) solution and, as the catheter is inserted by grasping the collar and not the catheter itself, non-sterile gloves can be used for insertion. The time taken to perform a DUEC test is approximately 2 min. In contrast the cost of a full urodynamic system is about £10 000. The time taken to perform a cystometrogram is 20 min and there are the additional costs of catheters, cleaning and filling solutions and sterile gloves. There would be a significant cost saving if DUEC was proved useful as a screening technique with cystometry reserved for those in whom the diagnosis is in doubt, particularly before surgery.

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The immunoperoxidase localization of tumour markers in ovarian cancer: the value of CEA, EMA, cytokeratin and DD9

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Summary. Primary tumours from 40 patients with epithelial ovarian cancer, treated at St Thomas's Hospital over a 10-year period, were studied for the immunocytochemical expression of the following tumour markers in formalin-fixed paraffin embedded material: carcinoembryonic antigen (CEA), epithelial membrane antigen (EMA), cytokeratin (CAM 5·2), and DD9. An indirect immunoperoxidase staining technique was used. All of the tumours were positive for EMA and CAM 5·2, and 30% of them were positive for both CEA and DD9. The absence of CEA and DD9 may be of value in differentiating between metastatic abdominal adenocarcinomas of ovarian origin and those of gastrointestinal origin, but no indication of prognosis was obtained using these epithelial markers. The strong and widespread staining of all of the tumours for EMA suggests that this may be a useful marker for detecting metastatic or recurrent disease by immunoscintigraphy.

Ovarian carcinoma carries a poor prognosis and an unacceptably high mortality, largely because of the late stage with which women with this disease present. There were 4473 new cases of neoplasms of the ovary registered during 1984 in England and Wales (OPCS 1985), and 3932 deaths from ovarian cancer in the same year (OPCS 1988). One approach to the earlier diagnosis of ovarian cancer would be by screening, using one or more tumour markers. The most useful marker would need to be specific for the disease, universally expressed by ovarian tumours and easily detectable in the serum. Such a marker would be of value in screening for early stage disease, but none has as yet been found for epithelial ovarian tumours. Serum levels of CEA or of any of the other tumour markers including CA 125, that have been assessed for the diagnosis and management of ovarian carcinoma, have only limited value (Lambert 1987). Other possible roles for a tumour marker might be in identifying the ovary as the primary site of a secondary deposit of tumour presenting as a carcinoma of unknown origin, in predicting

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prognosis, in monitoring response to treatment, and in detecting tumour recurrence.

We decided to investigate the immunocytochemical expression of carcinoembryonic antigen (CEA) (Gold & Freedman 1965), epithelial membrane antigen (EMA) (Heyderman *et al.* 1979), cytokeratin (CAM 5·2) (Makin *et al.* 1984), and DD9 (Grant *et al.* 1985) to determine whether the expression of these markers might be of prognostic or diagnostic value.

We examined tissue in paraffin wax-embedded surgical blocks from 40 of the epithelial ovarian carcinomas treated at St Thomas's Hospital between 1970 and 1980. No borderline tumours were included.

A not uncommon problem is that of a patient who is found to have deposits of tumour throughout the peritoneal cavity with an unknown primary site, or with malignant ascites in which adenocarcinoma cells are found. It is not possible to differentiate between a metastasis from a colonic or an ovarian primary, either histologically or cytologically, and one would be reluctant to treat a patient with toxic chemotherapy when this may be inappropriate and of no benefit. Patients found to have an occult colonic tumour would be more likely to benefit from surgical intervention to prevent the unpleasant sequelae of obstruction and perforation, even though there are proven metastases.

The expression of CEA has been studied in ovarian tumours and has been detected in a variety of epithelial types. It has been suggested that CEA immunostaining may be of help in determining the primary site of abdominal tumours of unknown origin, or in distinguishing between serous and mucinous neoplasms (Charpin *et al.* 1982). Several antibodies have been raised against preparations of milk fat globule membranes (EMA and HMFG types). They detect a large mucin-like glycoprotein in a wide variety of tumours (Heyderman *et al.* 1979; Burchell *et al.* 1983; Heyderman *et al* 1985). Positive staining has been demonstrated in most ovarian epithelial tumours (Heyderman *et al.* 1979; Sloane & Ormerod 1981; Bradgate *et al.* 1989), and it has been suggested that its presence indicates epithelial origin (Ashorn *et al.* 1988).

Cytokeratin has been shown to be expressed by all epithelial ovarian tumours and has also been considered to be of value in differentiating between tumours of epithelial and non-epithelial origin (Ashorn *et al.* 1988).

The monoclonal antibody DD9-E7 was raised against the GER pancreatic exocrine carcinoma cell line (Grant *et al.* 1985). The epitope to which the antibody binds is expressed by all pancreatic adenocarcinomas studied by us (Heyderman *et al.* 1990) and by a variety of other epithelial neoplasms. These include adenocarcinomas from most sites, squamous carcinomas and salivary gland tumours. (E. Heyderman, unpublished data). In pancreatic adenocarcinomas the antibody recognizes a family of glycoproteins of 80–115 Kd molecular weight. These are distinct from NCA (non-specific cross-reacting antigen) (Mach *et al.* 1972; Von Kleist *et al.* 1972) and CEA. The epitope to which the antibody binds is not found in CEA or NCA2 (Burtin *et al.* 1973), but it is present in NCA, suggesting that they have a shared epitope (A. G. Grant, unpublished data).

Patients and methods

Paraffin wax-embedded tissue blocks from the tumours of 40 of the patients with epithelial ovarian carcinomas referred to the radiotherapy department of St Thomas's Hospital between 1970 and 1980 were retrieved from the routine surgical files. The patients ranged in age from 33 to 79 years (mean 56·5 years). Five patients were classified as FIGO Stage I, 16 as Stage II, 17 as Stage III, and two as Stage IV.

The cases were chosen from those with an unequivocal diagnosis of primary ovarian carcinoma, with enough material left in the blocks for review of the histology and immunostaining of several sequential sections, and adequate follow-up data. Material from six of the women with bilateral disease was available, and in all of them both tumours were of the same histological type. A total of 46 tumours was therefore assessed. They comprised 25 serous (four bilateral), five mucinous, four clear cell, eight endometrioid (one bilateral), and four poorly differentiated or undifferentiated (one bilateral) carcinomas. Sequential 4 μm sections of one representative block of each of the tumours were immunostained using an indirect immunoperoxidase technique (Heyderman 1983). The primary antibodies used were mouse monoclonal antibodies to CEA (Amersham International plc, Bucks), EMA (Dako Ltd, Bucks), CAM 5·2 (Beckton Dickinson, Oxford) and DD9-E7 (Grant *et al.* 1985). The secondary antibody was an affinity purified sheep anti-mouse immunoperoxidase conjugate (Amersham).

The positive control sections used were a colorectal carcinoma for CEA and CAM 5·2, a ductal carcinoma of the breast for EMA, and a primary adenocarcinoma of the exocrine pancreas for DD9. For the negative controls we used an irrelevant mouse monoclonal antibody to prostatic acid phosphatase, PASE/4LJ and in one case, we used that antibody pre-absorbed with prostatic acid phosphatase coupled to agarose beads (Haines *et al.* 1989).

Results

All of the 46 tumours were strongly positive for EMA (Figs. 1–4). In the clear cell tumours EMA staining was often cytoplasmic, as has been seen with the closely related HMFG antibodies (Bradgate *et al.* 1989), and less frequently they showed the lacy membrane pattern seen in clear cell hypernephromas (Heyderman, 1981) (Fig. 1). In all of the tumours, including the clear cell type, the EMA stain emphasized acinar differentiation, often where it was not easily seen in haematoxylin and eosin preparations (Fig. 2).

While all tumours has some staining for cytokeratin (CAM 5·2) (Fig. 5), the distribution of cytokeratin staining was often focal, with some negative areas. Included non-neoplastic mesothelium was always strongly positive.

Of the 46 tumours 14 were positive for both CEA and DD9 (Figs. 6–8). Of the five mucinous tumours four (80%) were positive for each of these markers and were the most strongly staining of all of the tumour types, with each acinus showing some positivity. Of the eight endometrioid tumours four (50%) were positive and each contained several foci positive for CEA and DD9, especially in areas of squamous metaplasia. Six of the 25 serous tumours (24%) were positive for both of these markers, they contained very few scattered positive cells, arranged singly or in small clusters. None of the tumours, including the mucinous adenocarcinomas was as strongly stained for CEA as was the control colorectal carcinoma. Where patients had bilateral ovarian neoplasms they were of the same histological type, and in all six patients both tumours either expressed or did not express CEA and DD9. Some of the tumours, particularly serous carcinomas, contained numerous granulocytes and/or macrophages which made interpretation of DD9 staining, present in these normal cells (Grant *et al.* 1985), more difficult (Fig. 8). The staining for DD9 was generally weak and focal, with mucinous tumours more strongly positive than others, and two mucinous tumours strongly positive.

There was no significant difference in survival between patients with CEA and DD9 positive tumours and those with CEA and DD9 negative tumours, using the log rank test ($\chi^2 = 0{\cdot}02$, DF = 1, $P = 0{\cdot}89$) (Fig.9).

All but one of the 46 tumours were negative with the control PASE/4LJ antibody, one serous cystadenocarcinoma was positive for PASE/4LJ, and the absorbed antibody was negative with this tumour (Haines *et al.* 1989). The tumour was otherwise unremarkable. It was positive for EMA and cytokeratin, and negative for CEA and DD9. This negative control is not a test of specificity, but confirms that positive staining is due to the first antibody, and not either to binding of the indirect peroxidase conjugate, or to endogenous peroxidase.

Discussion

Previous studies have shown large variations in the percentage of ovarian tumours positive for CEA (Table 2). This may be explained by the use in some studies of less sensitive techniques and polyclonal antisera, or by the use of a commercial CEA antibody (Dako), not pre-absorbed with the closely related cross-reacting substance NCA (CEX) (Table 2). In those studies, staining may have resulted from recognition of NCA instead of, or as well as, CEA (Nap *et al.* 1983). In addition while the diagnosis of muci-

Table 1. Immunoperoxidase staining of ovarian carcinomas*

	Serous	Mucinous	Endometrioid	Clear cell	Undifferentiated
EMA	25/25	5/5	8/8	4/4	4/4
CAM 5·2	25/25	5/5	8/8	4/4	4/4
CEA	6/25	4/5	4/8	0/4	0/4
DD9	6/25	4/5	4/8	0/4	0/4

*Number of positive/total number of tumours.

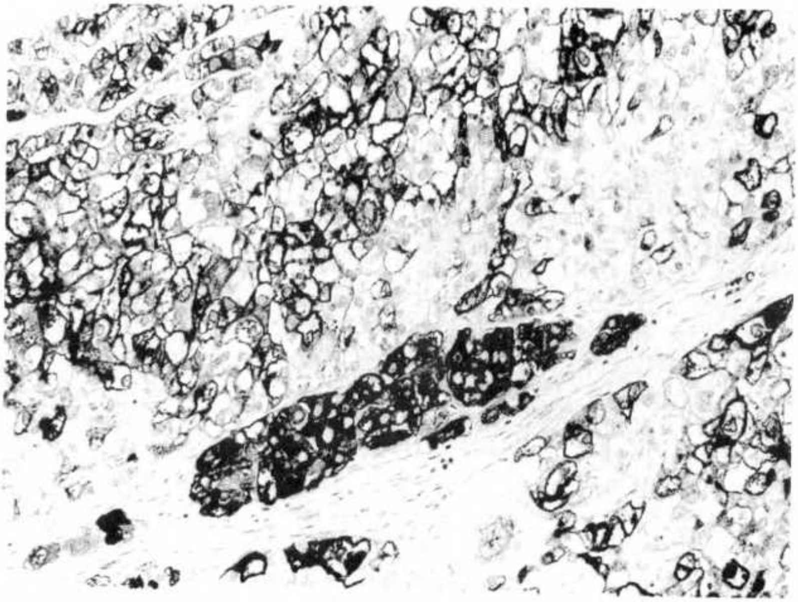

Fig. 1. Clear cell carcinoma stained for EMA showing a membrane lacy pattern of staining with a focus of cytoplasmic positivity. Indirect immunoperoxidase stains (Magnification × 240).

nous tumours is fairly clear cut, individual departments may be using slightly different histological criteria for the differential diagnosis of serous and endometrioid ovarian neoplasms.

In some studies none of the serous cystadenocarcinomas was positive for CEA, while in others, 19–82% were CEA positive. In some studies between 14 and 100% of the clear cell tumours were positive, but in others as also in our study these tumours were all negative (Table 2). In our study, and in another which used a polyclonal rabbit anti-CEA previously absorbed

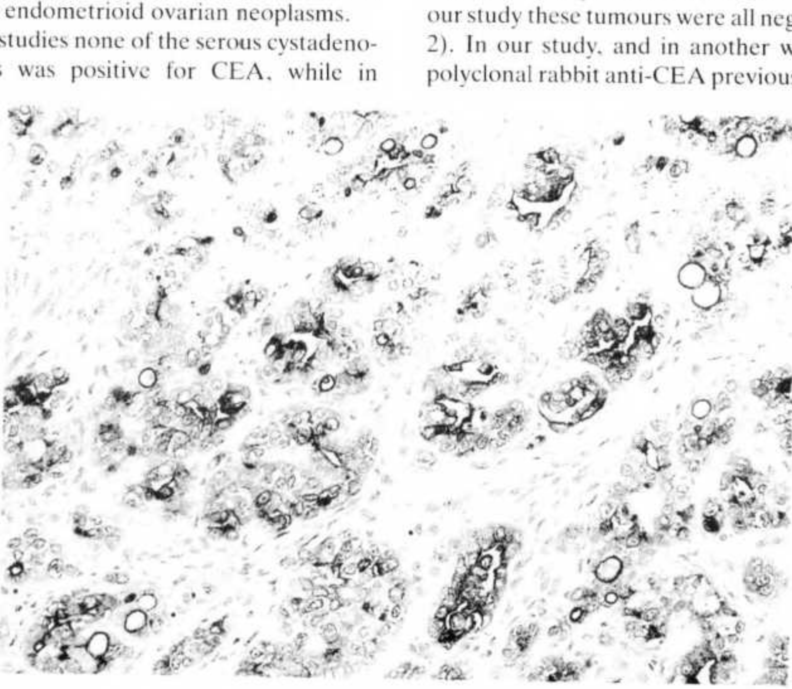

Fig. 2. Adenocarcinoma with many areas of apparently solid undifferentiated carcinoma. The micro-acinar pattern is shown up by the EMA immunostain. Indirect immunoperoxidase stains (Magnification × 240).

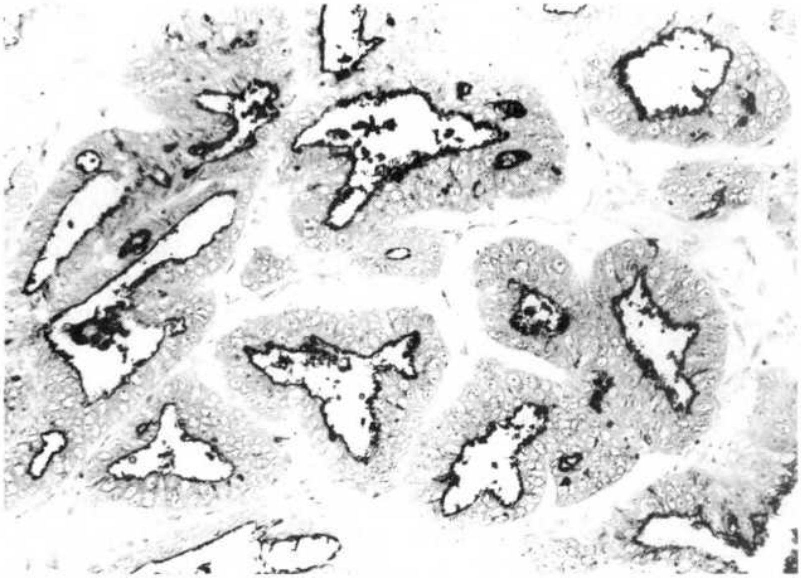

Fig. 3. Typical luminal pattern of EMA staining in an endometrioid carcinoma. Indirect immunoperoxidase stains (Magnification × 240).

with NCA (Fleuren *et al.* 1988), it was mainly foci of squamous metaplasia that were positive in endometrioid carcinomas.

When immunocytochemical techniques are to be used for diagnosis, each laboratory needs to perform pilot studies under the conditions of fixation appropriate for that department, with suitably specific antisera (Heyderman *et al.* 1989). Reliance on another group's published data to determine the significance of the presence of CEA could be misleading. Solutions to this major immunocytochemical problem include centralization of immunocytochemistry, which many would find unacceptable, more workshops

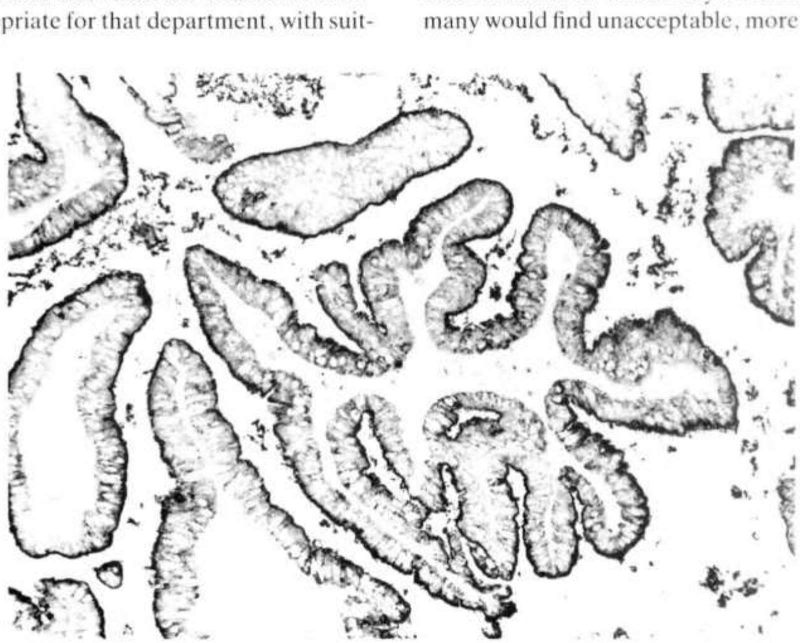

Fig. 4. Predominantly membrane staining for EMA in a papillary serous cystadenocarcinoma with some cytoplasmic positivity. Indirect immunoperoxidase stains (Magnification × 240).

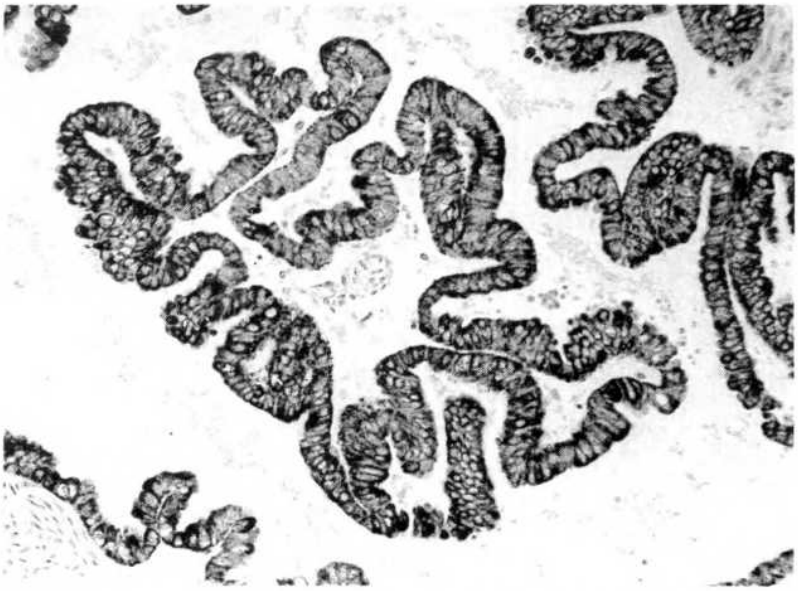

Fig. 5. The same tumour as in Fig. 4 stained for cytokeratin (CAM 5·2). The 'pericellular' pattern is well shown. Indirect immunoperoxidase stains (Magnification × 240).

to compare reagents and results, or the production of Department of Health guidelines on materials and methods.

In this department, all primary and metastatic adenocarcinomas of gastric or colorectal origin have stained positively for CEA. A CEA-negative adenocarcinoma in the abdomen in a woman, presenting as an adenocarcinoma of unknown origin, would be likely to be of ovarian origin, though metastasis from kidney, breast,

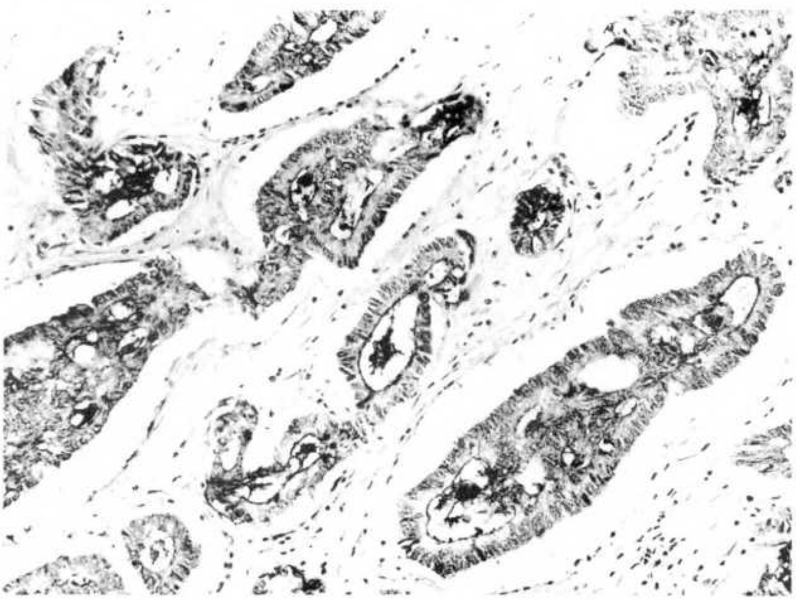

Fig. 6. Mucinous adenocarcinoma stained for CEA showing both luminal and cytoplasmic staining. Though very similar to the staining seen in colorectal carcinomas, in those tumours immunostains for CEA are usually stonger. Indirect immunoperoxidase stains (Magnification × 240).

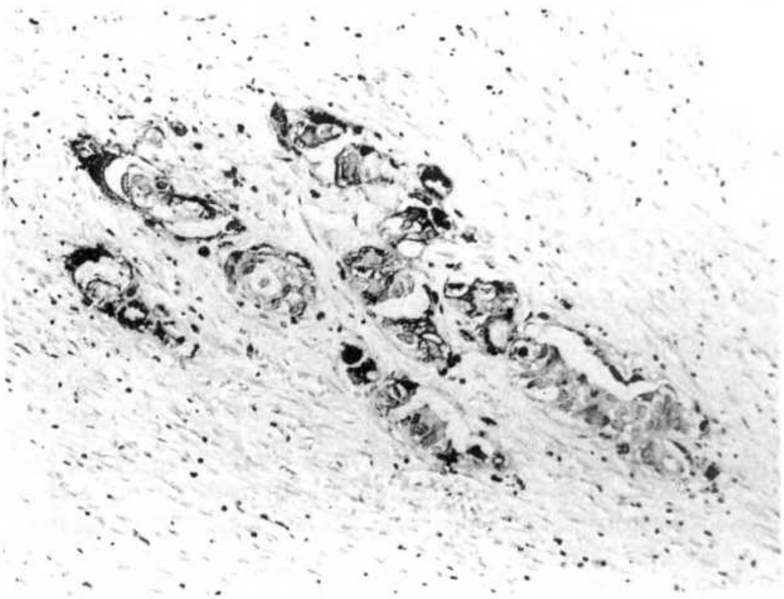

Fig. 7. Endometrioid carcinoma showing a focus of cytoplasmic positivity for DD9. Indirect immunoperoxidase stains (Magnification × 240).

lung, and pancreas (see below) would have to be excluded. In our study, 4 of 5 (80%) mucinous, 6 of 25 (24%) serous and 4 of 8 (50%) endometrioid cystadenocarcinomas were CEA positive, so that the presence of CEA neither indicates gastrointestinal origin nor excludes origin from the ovary. However, the staining in these ovarian tumours was weaker than in colorectal carcinomas, and the finding of only very occasional positive cells, as in the non-mucinous tumours, is rare in tumours of gastrointestinal origin. Weak or very focal CEA staining would be much more indicative of an ovarian tumour.

An important differential diagnosis lies

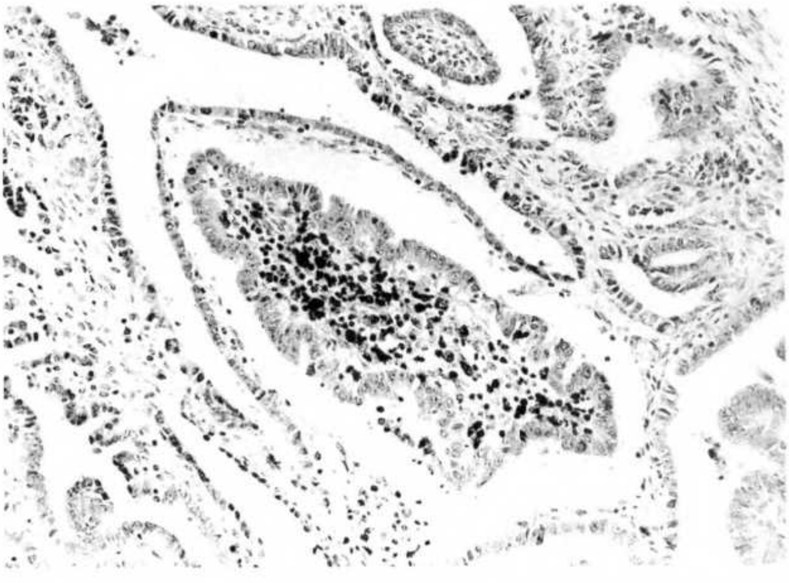

Fig. 8. A papillary serous adenocarcinoma showing weak focal cytoplasmic positivity for DD9, but strongly positive polymorphs and macrophages in the stroma of the papillary process (centre of figure). Indirect immunoperoxidase stains (Magnification × 240).

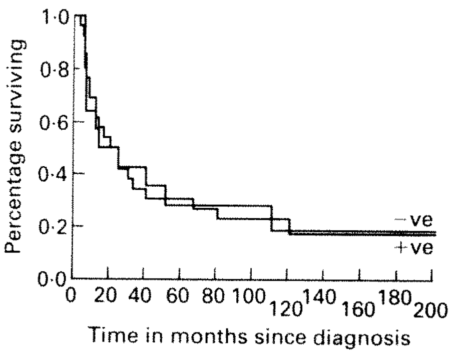

Fig. 9. Graph showing no statistical difference in survival between patients with CEA and DD9 positive and CEA and DD9 negative ovarian carcinomas (Log rank test. $\chi^2 = 0\cdot02$, DF = 1, $P = 0\cdot89$)

between clear cell adenocarcinomas of the ovary and of the kidney. Clear cell ovarian tumours in our study, as well as in most other studies, are CEA negative, as are renal cell carcinomas (Goldenberg *et al.* 1976), so that staining for CEA does not distinguish between them. However, CEA positivity in a clear cell carcinoma would virtually exclude kidney or ovary as a primary source. The pattern of staining for EMA in the ovarian clear cell carcinomas examined by us was partly cytoplasmic, rather than on the membrane as in renal cell carcinomas (Heyderman 1981), and this may be useful in differential diagnosis.

Peritoneal mesotheliomas are rare and the distinction from metastatic adenocarcinoma in biopsy material, which is a problem in the pleura, is not a common difficulty in the peritoneum. However, the cytological distinction between reactive mesothelial cells and adenocarcinoma in ascitic fluid may be very difficult. Both mesothelial cells and adenocarcinoma cells are EMA and cytokeratin positive (Makin *et al.* 1984; Heyderman & Ridley 1989), but mesothelium is negative for CEA (Wang *et al.* 1979), unless unabsorbed anti-CEA antibodies which cross-react with the shared NCA determinant are used (Silcocks *et al.* 1986). Demonstration of CEA positive cells is therefore indicative of the presence of epithelial (non-mesothelial) cells in peritoneal effusions, so that in this situation, where the normal cells are negative, CEA is acting as a specific tumour marker.

CEA is of no value in the distinction of benign from malignant ovarian tumours, since this marker has been identified in both unequivocally benign tumours as well as in borderline lesions. Its presence does not indicate either malignant transformation, or allow more precise classification (Heald *et al.* 1979; De Boer *et al.* 1981).

All of the tumours in this series were cytokeratin and EMA positive, and it has been concluded that these markers indicate epithelial origin in an otherwise undifferentiated neoplasm (MacDonald *et al.* 1988; Ashorn *et al.* 1988). While taken together with the morphology of the tumour, and the cellular distribution of staining, these markers may be of some value in diagnosis, cytokeratin has been demonstrated in tumours of mesenchymal origin (Norton *et al.* 1987), and EMA (HMFG) has been shown in synovial and epithelioid sarcomas, as well as in some neural tumours (Miettinen *et al.* 1984; Wick *et al.* 1988; Manivel *et al.* 1987). Vimentin has been shown to be co-expressed with cytokeratin in 7% of clear cell, 42% of serous, and 71% of endometrioid ovarian carcinomas (Dabbs *et al.* 1988), so its presence does not exclude epithelial origin. Cautious interpretation of the presence of these markers in an otherwise undifferentiated tumour is essential.

Second-look operations are performed in ovarian cancer to assess response to therapy, to resect residual disease following adjuvant therapy, or to detect recurrence. Radiolabelled HMFG2 monoclonal antibodies have been used in the diagnosis and assessment of ovarian cancer, and it has been suggested that immunoscintigraphy could obviate the need for second-look procedures (Shepherd *et al.* 1987). The strong widespread staining of all of the ovarian tumours in our series with the EMA antibody used in this study would suggest that it also might be useful for the imaging of recurrent or metastatic epithelial ovarian cancer.

Adenocarcinomas of the exocrine pancreas quite frequently present as metastatic deposits. DD9 has been demonstrated in all the pancreatic exocrine carcinomas so far studied (Heyderman *et al.* 1990). Its absence in abdominal deposits would make an occult pancreatic primary very unlikely, and an absent or weak stain for DD9 in a woman would be more in favour of an ovarian primary site.

The overall prognosis for the patients did not appear to correlate with expression of the markers that we investigated (Fig. 9), although this would have been difficult to detect in this study unless the differences had been very marked. Although initial staging may be inadequate, and

Table 2. Studies of the localization of CEA in ovarian cancer (epithelial tumours of borderline malignancy are included).

	Total		Muc		Ser		Endo		Clear		Undiff		Nos	
Study	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
*Marchand *et al* (1975)	15	(20)	3/7	(43)	0/8	(0)	—	—	—	—	—	—	—	—
*Goldenberg *et al* (1976)	12	(8)	1/5	(20)	0/3	(0)	—	—	—	—	—	—	0/4	(0)
*Rutanen *et al* (1978)	11	(0)	—	—	—	—	—	—	—	—	—	—	0/11	(0)
*Van Nagell *et al* (1978)	88	(9)	7/34	(21)	1/52	(2)	—	—	¶?/2	—	—	—	—	—
*Fenoglio *et al.* (1981)	98	(20)	10/18	(56)	0/31	(0)	6/15	(40)	0/8	(0)	10/26	(38)	—	—
*Kula *et al* (1983)	8	(100)	—	—	—	—	—	—	—	—	—	—	8/8	(100)
*Tohya *et al* (1986)	25	(44)	11/15	(73)	0/10	(0)	—	—	—	—	—	—	—	—
*Fleuren & Nap (1988)	60	(35)	5/14	(36)	0/16	(0)	9/10	(90)	0/4	(0)	0/16	(0)	—	—
†Puri *et al.* (1977)	7	(57)	2/2	(100)	0/2	(0)	1/1	(100)	—	—	—	—	1/2	(50)
†Heald *et al* (1979)	63	(86)	20/20	(100)	22/27	(82)	9/12	(75)	3/4	(75)	—	—	—	—
†De Boer *et al.* (1981)	15	(13)	1/6	17	0/5	(0)	1/2	(50)	0/2	(0)	—	—	—	—
‡Silcocks *et al.* (1986)	42	(69)	—	—	29/42	(69)	—	—	—	—	—	—	—	—
†Dabbs & Geisinger (1988)	54	(48)	7/8	(87)	10/19	(52)	4/7	(57)	5/13	(38)	—	—	0/7	(0)
†Neunteufel & Breitenecker (1989)	100	(32)	13/16	(81)	7/33	(21)	6/8	(75)	3/3	(100)	3/10	(30)	—	—
§Casper *et al* (1984)	137	(50)	31/39	(80)	10/52	(19)	17/25	(68)	7/9	(78)	3/12	(25)	—	—
‡Charpin *et al.* (1982)	57	(39)	21/24	(88)	0/20	(0)	3/10	(30)	1/7	(14)	0/6	(0)	—	—
‡Nouwen *et al* (1987)	39	(38)	3/4	(75)	8/19	(42)	1/7	(14)	0/2	(0)	—	—	—	—
‡Macdonald *et al.* (1988)	35	(37)	7/8	(88)	5/16	31	1/5	(20)	0/5	(0)	0/1	(0)	—	—
‡Present study	46	(30)	4/5	(80)	6/25	(24)	4/8	(50)	0/4	(0)	0/4	(0)	—	—

*Polyclonal antibody tested for lack of NCA activity.
†Polyclonal antibody not absorbed with NCA.
‡Monoclonal antibody
§Type of antibody not stated in the paper.
¶No results given in the paper.
Muc = Mucinous; Ser = Serous; End = Endometrioid; Undiff= Undifferentiated or poorly differentiated; NOS = Not otherwise specified.

repeat laparoscopy or laparotomy frequently results in upstaging of the FIGO classification, it is well recognized that the stage and the amount of residual tumour after initial surgery are the most important prognostic indicators in ovarian cancer (Smith *et al.* 1979). A much larger multicentre study of patients classified and treated according to strict protocols would be required to detect small differences.

We conclude that none of the markers studied here is specific for ovarian adenocarcinoma. Strong and widespread staining for CEA in a non-mucinous adenocarcinoma would be against the diagnosis of an ovarian primary, as would its presence in a clear cell carcinoma. The fact that EMA immunostains help to display malignant acini and indicate a diagnosis of adenocarcinoma in an otherwise undifferentiated carcinoma may be of value in ovarian pathology as well as in tumours from other sites (Heyderman *et al.* 1979). A 'pericellular pattern' of staining for cytokeratin is not seen in mesenchymal tumours, where there is cytoplasmic staining (Norton *et al.* 1987), so that a 'pericellular pattern' would be in favour of epithelial origin. A weak or absent immunostain for DD9 would make an ovarian primary site more likely than one of gastrointestinal or pancreatic origin, especially since the absence of DD9 in secondary deposits virtually excludes the diagnosis of metastatic adenocarcinoma of the exocrine pancreas

Acknowledgments

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A randomized controlled trial of early amniotomy

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Abstract

Objective—To determine if a policy of early amniotomy resulted in a reduction in mean labour duration when compared to a policy of conservation of the membranes.
Design—A single-centre randomized controlled trial.
Setting—A tertiary care teaching hospital in Alberta, Canada.
Subjects—Ninety-seven term nulliparae in spontaneous labour, baby in cephalic presentation.
Intervention——Early amniotomy versus intent to keep membranes intact.
Main outcome measures—Interval from randomization to delivery, rate of abnormalities of fetal heart rate tracings, cord artery blood pH, Apgar scores.
Results—The mean interval from randomization to delivery was 390·9 (SE 29·1) min in the amniotomy group and 442·9 (SE 34·1) min in the control group ($P = 0{\cdot}251$). There were no differences between groups in the occurrence of fetal heart rate tracing abnormalities, nor was there a difference in the proportion of babies with abnormal Apgar scores, or abnormal cord pH (< 7·20).
Conclusion—The results of the study fail to support the long held belief that early amniotomy is an effective method for reducing labour duration.

Amniotomy was introduced to obstetric practice by Kreis (1928) who, on the basis of data from case series, argued that it was an effective method to prevent prolonged labour. Amniotomy has recently been promoted as a component of the active management of labour, a protocol designed to reduce both the duration of labour and the occurrence of dystocia (O'Driscoll *et al.* 1984). The effects of amniotomy on the duration of labour have not been adequately assessed. The primary objective of this randomized trial of labour management was to determine the effectiveness of early amniotomy in reducing the duration of labour. The effects of the policy of membrane management on indicators of fetal and neonatal status were also assessed.

Subjects and methods

Subjects were eligible if they met the following criteria: nulliparous, spontaneous labour, single fetus in cephalic presentation, term pregnancy (⩾ 38 weeks), intact membranes, and a normal fetal heart monitor tracing at admission. Exclusion criteria were a history of genital herpes, the presence of proteinuria or hypertension, or a cervical dilatation of ⩾ 5 cm at admission. Demographic information on eligible non-participants was obtained from the hospital's computerized data base.

The study was approved by the University

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Medical Ethics Committee and consent was obtained at the time of admission. A non-stratified randomization technique was employed using the block method of Zelen (1974). A series of numbered, sealed, opaque envelopes was prepared containing allocation. Allocation was later verified against the master list. Women with cervical dilatation of < 3 cm were randomized when the fetal head was fixed in the pelvis and the cervix had undergone a change in dilatation after admission. Women with a cervical dilatation of ≥ 3 cm were randomized when the fetal head was fixed in the pelvis.

Women in the amniotomy group underwent the procedure as soon as possible while those in the control group had membranes conserved unless intervention was dictated by the judgment of the treating physician. Amniotomy during labour was permissible in the control group if there was a fetal heart rate abnormality, if there had been an arrest of cervical dilatation for ≥ 2 h, or when full dilatation was achieved. Physicians were requested not to augment labour with oxytocin unless there had been an arrest of cervical dilatation for ≥ 2 h. The frequency and duration of post-randomization electronic fetal monitoring was left to the treating physician. The time from randomization to delivery was the outcome of interest.

Fetal heart rate tracings were later analyzed by two trained observers who worked independently and who were blinded to allocation. The following definitions were used as guidelines in the interpretation of the tracings. Bradycardia: < 110 bpm; tachycardia: > 160 bpm; decreased variability: ≤ 5 bpm about baseline. Decelerations were classified as (1) early≥ 10 bpm below the baseline rate, onset within 20 s of the onset of contraction, recovery to baseline rate within 20 s of the end of the contraction; (2) late: repeated decreases in fetal heart rate, onset > 20 s after onset of contractions, recovery to baseline rate > 20 s after end of contraction; (3) variable: sharp decrease in rate from baseline and a variable relation to contractions. These were subclassified as (i) severe variable—one of the following criteria had to be met: ≥ 60 s duration, ≥ 60 bmp below baseline; a rate of < 60 bmp at its lowest point; (ii) mild variable: ≥ 15 bpm below the baseline and ≥ 15 s duration but failing to meet the criteria for severe variable decelerations. Variable-type decelerations which were < 15 s duration were disregarded Repeated variable decelerations were counted as separate events only if the fetal heart rate returned to the baseline between decelerations. A dichotomous outcome (normal versus abnormal) was assigned to each hour during which at least 10 min of interpretable tracing was obtained. The segment of tracing was considered 'abnormal' if any of the following features were noted: decreased variability, severe variable or late decelerations, baseline tachycardia or bradycardia. The proportion of 'abnormal' hours was determined for both the pre-randomization and post-randomization periods. For each hour of tracing, the two observers were considered to agree on interpretation if the difference between observers in the total number of decelerations counted for that hour was no more than one, and if there was complete agreement on the normality or abnormality of the baseline fetal heart rate and of its variability. There was agreement between the observers for 87·5% of the hours assessed. When there were disagreements, the tracings were reviewed by the two observers together and a consensus on the interpretation of the tracings was achieved for all hours.

Umbilical artery blood was collected in a heparinized syringe by the delivery physician and was analyzed on a Corning Blood Gas Analyzer within 30 min of delivery. The Apgar score was assigned by the delivery room nurse or by a member of the paediatric staff, if one was present at delivery.

The comparisons of group means were performed using Student's *t*-test. The χ^2 test was used for comparison of proportions, except where the expected value for a cell was less than 5. In this case Fisher's exact test was used. The multiple linear regression analyses used Minitab (Ryan 1985). BMDP-2L (Hoplans 1985) was used to apply Cox's proportional hazards model to the survival data. The power analysis was performed using the statistical package Power (1985).

Results

The study was conducted at Foothills Hospital, a tertiary care teaching centre associated with the University of Calgary, between Sept 11, 1987 and Sept 11, 1988. Of the 1503 nulliparous women delivered during the study period, 278 (18%) were eligible to participate. The reasons for ineligibility and their frequencies are shown in Table 1. Of the 278 women eligible to partici-

Table 1. Reasons for exclusions in 1503 nulliparous women delivered during the study period

	N	(%)
Total no. of women delivered	1503	(100)
Total no. excluded		
Reasons for exclusion:	1225	(81·5)
Spontaneous rupture of membranes	373	(24·8)
Induction of labour	335	(22·3)
Cervical dilation > 5 cm at admission	113	(7·5)
Malpresentation	67	(4·5)
< 266 days gestation	157	(10·4)
Suspected fetal distress	52	(3·5)
Other (including med complication)	128	(8·5)
Total no. eligible	278	(18·5)

pate 97 (35%) entered the study. The reasons for non-participation of eligible women were patient refusal (44%), doctor refusal (5%) and failure to offer participation by the nursing staff (16%). The mean gestational age at delivery was 39·9% (SD 0·1) weeks for non-participants and 40·0 (SD 0·1) weeks for participants. The mean maternal age was 27·5 (SD 0·3) years for non-participants and 26·7 (SD 0·6) years for participants. Oxytocin use for labour augmentation was similar in the two groups (non-participants 27·6%, participants 30·9%), as was the frequency distribution of the methods of delivery (data for non-participants not shown). A total of 100 women were randomized, 49 to the amniotomy group and 51 to the control group. Eligible patients did not change treatment groups after randomization, regardless of the evolution of their membrane status. Three women who did not meet the eligibility criteria were randomized in error (1 breech, 2 inductions of labour). Of the 97 eligible women who were randomized, 47 were allocated to the amniotomy group and 50 to the control group (conservation of the membranes). As seen in Table 2, the mean prepregnancy weight, the mean admission weight and the mean birthweight were somewhat greater in the amniotomy group than in the control group. The groups were similar with respect to maternal height education, and gestational age. The mean cervical dilatation at admission was somewhat less in the amniotomy group than in the control group (Table 2). A similar proportion of women in the two groups smoked during pregnancy, attended prenatal classes, was accompanied by a significant other (usually the husband), and claimed English as their mother tongue (data not shown).

Of the 47 women in the amniotomy group two had a spontaneous rupture of the membrane before amniotomy. Of the 50 women in the control group 19 had an amniotomy before full dilatation. The indications for amniotomy in the control group were labour augmentation (11), and suspected fetal distress (8). The mean interval from labour onset to rupture of the membranes was 431 (SE 36) min in the amniotomy group and 592 (SE 37) min in the control group ($t_{95df} = 3{\cdot}13$, $P = 0{\cdot}002$). Figure 1 is an histogram of the distribution of cervical dilatations at the time of membrane rupture for the two groups. Of the women in the control group 60% achieved $\geqslant 8$ cm cervical dilatation before membrane rupture compared with only 2% in the amniotomy group.

Fifteen women in each group had labour augmented with oxytocin. There were eight caesarean sections in the amniotomy group and four in the control group. Similar proportions of women in each group were delivered by low forceps or vacuum extractor (amniotomy 23%, control 28%), and by mid-forceps (8% in each group).

The mean interval from randomization to

Table 2. Maternal demographic data for study patients. amniotomy and control groups

	Amniotomy ($n = 47$)		Control ($n = 50$)	
	Mean	(SE)	Mean	(SE)
Years of education	13·3	(0·3)	14·3	(0·4)
Prepregnancy weight (kg)	61·1	(1·75)	57·3	(7·1)
Admission weight (kg)	76·3	(1·7)	71·8	(1·0)
Height (cm)	164·8	(0·9)	165·3	(0·9)
Birthweight (g)	3493·1	(73·0)	3322·1	(64·0)
Gestational age (days)	281·1	(0·8)	279·5	(1·0)
Cervical dilatation first exam (cm)	2·4	(0·02)	2·8	(0·02)
Onset of labour to randomization (min)	399·0	(31·0)	331·0	(28·0)

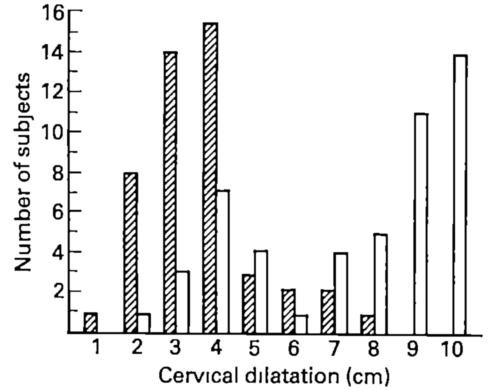

Fig. 1. Frequency distribution of cervical dilatation at the time of rupture of membranes in amniotomy (shaded) and control (unshaded) groups.

delivery was 390·9 (SE 29·1) min in the amniotomy group and 442·9 (SE 34·1) min in the control group ($t_{95df} = 1{\cdot}15$, $P = 0{\cdot}251$). A further analysis of labour duration was based on a subgroup of women who had vaginal deliveries. The mean duration of labour and the sub-intervals of labour for these women are displayed by treatment group in Table 3. The interval from randomization to full dilatation did not differ significantly between the two groups.

The greater mean values for maternal weight at admission and birthweight and the lower mean cervical dilatation at admission in the amniotomy group could have biased toward longer labours in that group. The relations between these variables and the interval from randomization to delivery in the women delivered vaginally were investigated by multiple linear regression (Table 4). The regression coefficients that are expressed for each variable were obtained by entering that variable as the last one in the regression equation. The treatment policy of membrane management was not a statistically significant predictor of the duration of the interval

To better describe the behaviour of the two treatment groups with respect to the interval from randomization to delivery, survival curves were created. For the purposes of this analysis, the critical event was defined as vaginal delivery Women delivered by caesarean section were considered as censored following the procedure. Cox's proportional hazards model was applied to the data to control for differences in co-variates that could influence labour duration. The variables included in the model along with their regression coefficients are shown in Table 5. A positive coefficient indicates an increase in the hazard function and an inverse relation with survival (continuation in labour). The graphic representations of the adjusted estimates of the survival functions are shown in Fig 2. Trial status (amniotomy versus conservation of the membranes) was not a statistically significant predictor of survival function, adjusting for birthweight, cervical dilatation at admission and maternal admission weight.

With respect to maternal post-partum morbidity, no women required blood transfusion. One woman in the amniotomy group developed a wound cellulitis after caesarean section and was treated with oral antibiotics. No woman met the study criteria for febrile morbidity (two episodes of fever > 38° C on two occasions, excluding the first 24 h after delivery).

Fifty five women in the amniotomy group and 47 women in the control group had post-randomization fetal heart tracings. The mean duration of electronic fetal monitoring was similar in the two treatment groups (amniotomy: 7·73 SE 0·47 h; control: 8·57, SE 0·48 h). Concerning the dichotomous fetal heart rate tracing outcome, the mean proportion of hours during which the tracings were 'abnormal' was similar in the two groups (post-randomization: amniotomy: mean 0·41, SE 0·05; control mean 0.44, SE 0.04; $t = 0{\cdot}50$, $P = 0{\cdot}620$).

The two treatment groups were similar with respect to the frequency of early, mild variable, severe variable and late decelaration during the pre-randomization period. The mean hourly

Table 3. Duration of labour (minutes) in women delivered vaginally in the amniotomy and control groups

	Amniotomy (n = 39)		Control (n = 46)				
	Mean	(SE)	Mean	(SE)	t	df	P
Onset-delivery (min)	776	(52)	763	(48)	0·21	83	0·842
Onset-admission (min)	201	(26)	192	(31)	0·21	83	0·842
Admission-randomization (min)	192	(29)	149	(16)	1·37	83	0·175
Randomization to full dilatation (min)	311	(20)	346	(30)	0·82	83	0·422
Second stage (min)	72	(9)	75	(6)	0·24	83	0·807

Table 4. Multiple linear regression examining several variables for effect on interval from randomization to delivery in the women delivered vaginally

Variable	Regression coefficient	*t*-ratio	*P*
Constant	264·7		
X1			
Birthweight	0·14	2·88	0·005*
X2			
Cervical dilatation at admission	−39·10	−1·71	0·091
X3			
Maternal admission weight	−2·64	−0·98	0·332
X4			
Trial status (0 = control, 1 = amniotomy)	−80·10	−1·67	0·099

Interval (randomization to delivery) = 264·7 + 0·14(X1) − 39·1 (X2) − 2·64 (X3) − 80·10 (X4)

*Significant at the alpha = 0·01 level

rates of the four types of deceleration during the post-randomization period are shown in Table 6. There were no statistically significant differences between the two groups in the rates of deceleration after randomization.

The results of the variables which are indicators for condition at birth are summarized in Table 7. The proportions of babies with a 1-min Apgar score of < 6 and a 5-min Apgar score of < 8 did not differ significantly between the two groups Umbilical artery blood pH was measured in 42 of the 47 babies born in the amniotomy group and in 47 of the 50 babies born in the control group. No statistically significant difference was found between the two groups in the proportion of infants with pH < 7·20. The mean cord artery pH was 7·254 (SE 0·07) in the amniotomy group and 7·256 (SE 0·08) in the control group. Six infants in each group were provided with assisted ventilation at birth. Neonatal cephalohaematoma was considered present if the diagnosis was recorded in the baby's chart by the treating physician This occurred in one infant in the control group who was born by mid-forceps after a prolonged second stage. There was no abnormality noted on skull x-ray. This infant was cared for in the normal nursery and was discharged from hospital without further complications. All babies left hospital alive and in good condition

Discussion

Several controlled studies which assess the effect of amniotomy on labour duration have been reported. Schwarcz & Caldeyro-Barcia (1982) reported a multi-centre study of 1124 nulliparous and multiparous women. The mean duration of the active phase of labour (5 cm to full dilatation) was 165 min in women who had an amniotomy compared with 213 min in a control group (P < 0·001, effect size = 0·77). This study suffers from methodological problems as recently reviewed by Keirse (1989). A smaller randomized trial by Stewart *et al.* (1982) found mean labour duration (admission to full dilatation) to be 4·9 h in the experimental group and 7·0 h in the control group (P < 0·02, effect

Table 5. Analysis using Cox's proportional hazards model to assess the effects of variables on survival function

Variable	Coefficient	Coefficient/SE	*P*
X1			
Birthweight	−0·001	−2·476	0·013*
X2			
Cervical dilatation at admission	0·118	1·158	0·2468
X3			
Maternal admission weight	0·012	1·005	0·3188
X4			
Trial status (0 = control,	0·231	0·960	0·337

* Significant at the alpha = 0·05 level.

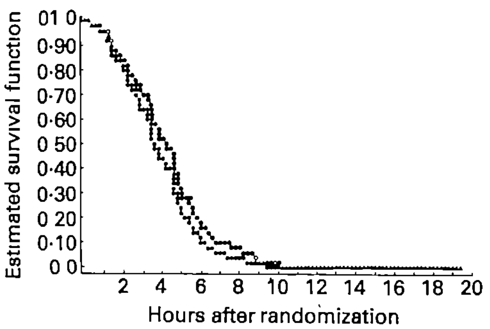

Fig. 2. Estimated probability of continuation in labour for each hour following randomization using Cox proportional hazards model (Amniotomy—closed circles, control—open circles.)

size = 0·7). The authors did not stratify for parity in the analysis. Two smaller studies by Wetrich (1970) and Laros (1972) reported similar results.

In that our study was designed to assess the effectiveness of a commonly used obstetrical procedure in a low risk population, it was surprising that the proportion of women who were eligible to participate was so small. The high number of exclusions was, in part, a function of the study having been performed in a tertiary care centre. There was a significant number of refusals by eligible patients, the reasons for which were not assessed. Because recruitment was completed in early labour, it was considered important that women be informed that they were free either to participate or not to participate. Our ability to compare study participants with eligible non-participants is limited by the few variables which were measured in the non-participant population. However, the available data suggest the two groups were similar.

In the course of the main analysis, differences between the treatment groups were identified on several co-variates. This is a cause for caution in the interpretion of the results. The comparisons regarding labour duration which are first presented are based on the unadjusted data. In general, the adjusted analyses served to support the conclusions which had been made on the basis of the unadjusted comparisons. With respect to the duration of labour, comparison of the unadjusted as well as the adjusted means provides no support for rejection of the null hypothesis. The analyses based on the survival curves further strengthen these conclusions.

The initial sample size calculation was based on the formula $n = 2(Z\alpha + Z\beta)^2/(\log_e E)^2$ where E is the effect size (Donnor, 1984). E = 0·7 was used for this calculation. This formula, which is designed for survival analyses and does not take into account the dispersion of the data, yielded a sample size requirement of 110 subjects/group. Because of limited resources, a power analysis was performed after 97 subjects had been recruited using a formula which takes into account both the dispersion of the data and the group means that had been attained. The calculation indicated that a power of 0·85 had been achieved for the specified effect size (0·7). It was decided to terminate the study at that point. It should be noted, however, that the power of the study to detect a 20% reduction in labour duration was only 0·55.

Many of the women in the current study were randomized when cervical dilatation was < 3 cm. This may partially explain the discrepancy between the findings of the current study and that of previous clinical trials when women were randomized later in labour. Further studies of this type should stratify by cervical dilatation at the time of randomization to assess whether any observed effect on labour duration is dependent on the cervical dilatation at the time of the procedure.

Several previous reports have suggested an association between early amniotomy and the occurrence of fetal heart rate decelerations. Schwarcz *et al.* (1973) found that after amniotomy over 20% of contractions produced type I

Table 6. Mean hourly rates of early, mild variable, severe variable, and late decelerations during the post randomization period for patients in the amniotomy and control groups

	Amniotomy		Control				
Type of deceleration	Mean	(SE)	Mean	(SE)	*t*	df	*P*
Early	0·41	(0·17)	0·49	(0·23)	0·32	90	0·750
Mild variable	1·10	(0·20)	1·50	(0·32)	1·23	90	0·220
Severe variable	1·61	(0·33)	2·83	(0·61)	1·73	90	0·084
Late	0·32	(0·22)	0·54	(0·40)	0·47	90	0·640

Table 7. Indicators of early neonatal status for infants born in the two study groups

	Amniotomy		Control		Fisher's exact
	Total no.	No. affected (%)	Total no.	No. affected (%)	*P*-value
Apgar 1 min < 6	47	7 (14·9)	50	9 (18·0)	0·787
Apgar 5 min < 8	47	2 (4·3)	50	5 (10·0)	0·437
Cord artery blood pH < 7·20	42	8 (17·0)	47	6 (12·0)	0·566
Assisted ventilation	47	6 (12·8)	50	6 (12·0)	1·000
Admitted to intensive care nursery	47	1 (2·1)	50	2 (4·0)	1·000

(early) decelerations, as opposed to 3% of contractions before membrane rupture.

Baumgarten (1976) reported the occurrence of early decelerations to be approximately doubled in women undergoing amniotomy relative to those labouring with membranes intact. Aladjem & Miller (1977) in an observational study found that spontaneous or artificial rupture of the membranes produced transient FHR abnormalities in approximately 25%, mainly early decelerations. By 15 min after rupture of membranes, there were no differences between groups in the occurrence of FHR abnormalities. Stewart *et al.* (1982), on the other hand, failed to show any differences between treatment groups in the rate of FHR tracing abnormalities, although the methods used to classify the tracings were not clearly specified.

With respect to the effects of early amniotomy on neonatal outcome, Schwarcz *et al.* (1982) found no association between the state of the membranes and Apgar score or neurological condition at 48 h of life. Baumgarten (1976) and Stewart *et al.* (1982) found no differences between groups in Apgar scores or in cord artery blood pH. Martell *et al.* (1976), in a study of 38 patients, reported early membrane rupture to be associated with a lower mean cord artery blood pH than occurred in infants of patients who laboured with intact membranes.

There are several advantages of the current study over previous studies with respect to indicators of fetal and neonatal status. The randomization process was carefully blinded, and the methods of classification of the FHR tracings was clearly specified. The dichotomous FHR tracing outcome selected as abnormal only those findings which could be of clinical significance to obstetrical decision making. As is appropriate in the analysis of management trials, the participants remained in their respective groups despite the post-randomization evolution of membrane status. Although this approach increases the risk of beta error, the absence of trends in the data suggests that it is unlikely that larger studies would demonstrate differences between treatment groups in fetal status or in neonatal outcomes.

In conclusion, the results of this study fail to support the longheld belief that early amniotomy is an effective method to reduce labour duration. A multicentre trial designed to further assess the effects of the procedure on labour progress is underway.

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Growth hormone excess and galactorrhoea without acromegalic features. Case reports

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Case Reports

Patient 1

A 31-year-old woman presented in 1985 with a 6-year history of galactorrhoea and oligomenorrhoea. Clinical examination was normal apart from a superior bitemporal quadrantanopia and expressible galactorrhoea. In particular there were no features of acromegaly. The serum prolactin (PRL) was slightly elevated at 40 µg/l (normal <20) and a CT scan showed a pituitary macroadenoma with suprasellar extension. A 4-week trial of bromocriptine 2·5 mg twice daily had no effect upon her galactorrhoea despite prolactin falling to 2 µg/l. Growth hormone (GH) remained elevated at 22–30 µg/l. She was therefore referred for surgery. At that time the free thyroxine (T4) was 16 pmol/l (normal 13–32) thyroid stimulating hormone (TSH) 1·0 mU/l (normal <5), LH 7 IU/l (normal <5) and PRL 2 µg/l. Basal GH was 30 µg/l (normal <5) and did not suppress during an oral glucose tolerance test (Table 1). The capacity of the patient's sera to bind iodinated GH was normal at 14·2% of ^{125}I-hGH bound/100 µl serum (normal range 12–20%) (Herington *et al* 1986). Trans-sphenoidal tumour clearance was performed and histology demonstrated a chromophobe adenoma. Immunoperoxidase staining showed that most adenoma cells were positive for GH with infrequent cells weakly positive for PRL. Electronmicroscopic examination revealed a monomorphous pituitary adenoma composed of large oval cells with interdigitations between adjacent cells (Fig. 1). The cytoplasm was abundant, containing prominent smooth and rough endoplasmic reticulum, and moderate numbers of mitochondria (Fig. 2) Secretory granules were sparse, uniformly electron-dense, with discrete limiting membranes. Granules were small, averaging 45 nm in diameter, and were found around the periphery of the cells. No exocytosis was seen (Fig. 1).

Post-operatively the galactorrhoea resolved and menses returned to normal. Serum free T4, TSH, LH, FSH, and PRL were normal. An oral glucose tolerance test performed in July 1987 showed mildly elevated basal GH of 5 µg/l with GH suppressing to 2·5 µg/l (Table 1) and a slightly elevated insulin-like growth factor (IGF)-1 at 2·2 U/ml GH-binding capacity was 14%. In January 1988 an 8 h GH secretory profile (samples taken every 30 min from 0800 to 1600 h) and IGF-1 were normal.

Patient 2

In January 1986 a 19-year-old woman was admitted for surgical therapy of a pituitary tumour. A 14-month history of galactorrhoea and headaches was antedated by irregular menses since menarche at the age of 13. Investigations performed 8 months before admission showed an elevated serum PRL of 36 µg/l and a definite pituitary microadenoma on CT scan. Since an 8 month trial of bromocriptine (7·5 mg daily)

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Table 1. Growth hormone levels basally and after an oral glucose tolerance test (OGTT), and serial basal prolactin levels measured before and after operation in the three patients

	Growth hormone (μg/l) before and after OGTT (min)								Prolactin (μg/l)		
Time (min)	−30	−15	0	30	60	90	120	180	−30	−15	0
Patient 1											
Before	–	30	23	23	25	24	24	22	2	3	<2
After	–	5	4	4	4	3	2	3	12	14	13
Patient 2											
Before	42	39	35	–	–	–	–	–	21	22	15
After	–	8	3	2	0·5	0·5	0·5	<0·5	12	12	11
Patient 3											
Before	–	23	18	14	14	14	14	18	20	19	18
After	2	1	3	1	<1	<1	1	1	5	8	6

Normal basal levels· Growth hormone <5 μg/l, Prolactin <20 μg/l.
Post oral OGTT: Growth hormone <2·5 μg/l.

failed to suppress the galactorrhoea with prolactin levels at 15–20 μg/l, she was referred for surgical therapy. Her examination was remarkable only for persisting expressible galactorrhoea despite bromocriptine therapy. There were no features of acromegaly. Preoperative investigations included normal free T4 21 pmol/l, TSH 4 mU/l, FSH 2 IU/l and LH 2 IU/l. Serial fasting GH levels were 84, 77 and 70 mU/l for three samples taken over 30 min (normal <10) and normal GH-binding protein capacity (13·7%). At trans-sphenoidal surgery a right sided microadenoma was identified and enucleated. However, histology failed to demonstrate a definite adenoma, but pituitary tissue showed an increased number of cells staining for GH and PRL with immunoperoxidase. Her menses returned to normal post-operatively but minor expressible galactorrhoea persisted. In July 1987 serum PRL was 12 μg/l, FSH 2 IU/l, LH 8 IU/l, serum GH 7 μg/l with normal suppression on oral glucose tolerance testing to <2·5 μg/l and IGF-1 1·0 U/ml. CT scan was normal. The GH-binding capacity of her serum remained unchanged at 13·8%.

Patient 3

A 27-year-old woman presented in November 1988 with galactorrhoea for 5 years and occipital headaches for 1 year. At the time she was taking the contraceptive pill (Brevinor) and no other medication. She had given birth to a healthy baby boy 20 months previously. Clinical examination was normal other than expressible galactorrhoea. Clinical signs of acromegaly were absent. Serum PRL was elevated at 29 μg/l. GH was not measured. A CT scan demonstrated a pituitary macroademona with suprasellar extension (1·5 cm diameter) The contraceptive pill

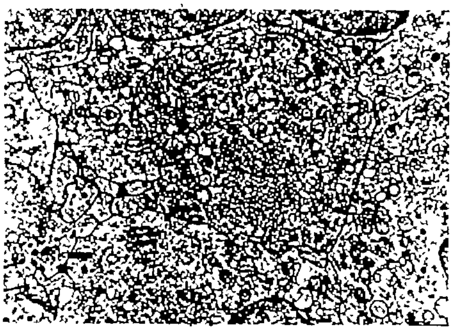

Fig. 1. Electron micrograph showing interdigitation between membranes and prominent smooth endoplasmic reticulum × 9000 Scale bar = 1 μ (patient 1).

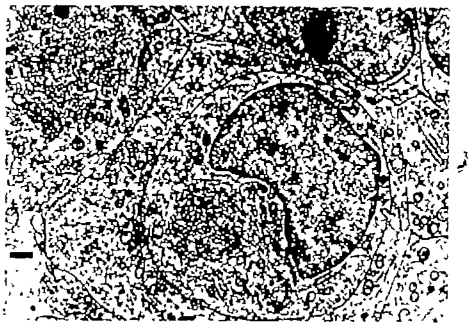

Fig. 2. Electron micrograph of adenoma cells containing prominent smooth endoplasmic reticulum and golgi apparatus × 8200 Scale bar = 1 μ (patient 1)

was stopped and she was treated with bromocriptine, 2·5 mg twice daily. Four months later the serum PRL had fallen to <2 μg/l, but her symptoms of oligomenorrhoea and galactorrhoea persisted and a repeat CT scan revealed no change in the size of the tumour.

She was referred for further assessment in June 1989, having stopped the contraceptive pill three months earlier. Her periods were irregular and the serum PRL was 20 μg/ml when not taking bromocriptine. Basal hGH was elevated at 26 μg/l (mean of three basal samples) and did not suppress following an oral glucose tolerance test (Table 1). GH-binding capacity was low at 5·7%, IGF-1 was raised at 4·8 U/ml (normal <1·9). Other hormone levels were within normal limits: TSH 0·6 μU/l, free T4 20 pmol/l, FSH 4 mU/ml, LH 3·9 mU/ml. She was treated with the long acting somatostatin analogue Sandostatin (Octreotide, Sandoz company), 100 μg three times daily subcutaneously for 8 weeks. In this time she had one menses and her headaches and galactorrhoea were less pronounced. GH remained elevated at 22 μg/l and IGF-1 was 3·3 U/ml. As CT scan showed no change in tumour size and GH levels failed to suppress, trans-sphenoidal surgery was performed revealing an abnormally soft macroadenoma. Histology confirmed a mixed acidophilic chromophobe adenoma. The adenoma cells stained strongly for GH but not for PRL or other hormones with immunoperoxidase. Post-operatively her headaches and galactorrhoea resolved, and menses returned to normal. Serum GH was 1–3 μg/l with a binding capacity of 16·0%, and a normal IGF-1 (1·6 U/ml).

Methods

TSH, LH, FSH, PRL and GH were assayed by standard double antibody radioimmunoassays. Standards employed in these assays were TSH: MCR 68/38; LH and FSH: WHO 69/104; prolactin: NIH 75/504, and growth hormone: CSL BS002. The sensitivities of the respective assays were : TSH 0·5 IU/l, LH 0·4 IU/l, FSH 0·7 IU/l, prolactin 1·0 μg/l and GH 0·5 μg/l (Best *et al.* 1982, Crock *et al.* 1988). IGF-1 was assayed by the method of Silbergeld *et al.* (1986) and human GH-binding protein was assayed as described previously (Herington *et al.* 1986). Light microscopy biopsy specimens were fixed in 10% buffered formalin and processed through paraffin. Dewaxed sections were stained with haematoxylin and eosin and PAS-Orange G. Immunoperoxidase staining for a panel of anterior pituitary hormones was by the methods described by Sternberger (1974)

Discussion

The present three patients, together with those reported previously (Table 2), represent an unusual presentation of GH excess, characterized by galactorrhoea and oligomenorrhoea without somatic features of acromegaly. The unique features of the present report include studies performed to confirm that the presenting symptoms were secondary to GH excess rather than PRL excess, and the determination of GH binding capacity to examine the cause of the discrepancy between growth promoting and immunoreactive GH activity.

In patients with galactorrhoea and menstrual irregularity associated with GH excess, features of acromegaly are usually present (Melmed 1986). These symptoms are usually secondary to cosecretion of PRL but may be due to excess GH alone (Fradkin *et al.* 1989). Recently galactorrhoea and menstrual irregularity were described in patients without traditional clinical features of acromegaly despite the GH excess (Tourniaire *et al.* 1985; Klibanski *et al.* 1987). The absence of somatic features were ascribed to the short duration of symptoms prior to presentation, and the cause of the presenting symptoms was uncertain because the patients had significant elevations of both GH and PRL (Tourniaire *et al.* 1985; Klibanski *et al.* 1987).

In this report, suppression of PRL using bromocriptive (noting that GH remained elevated) had no effect upon our patients' galactorrhoea or irregular menses. However, when the GH excess was partially reversed by Sandostatin or completely reversed by surgery, galactorrhoea resolved in patients 1 and 3, and menses became regular in all patients. Since GH excess may produce galactorrhoea (Fradkin *et al.* 1989), it is likely that the presenting symptoms were related to GH hypersecretion.

The absence of somatic features cannot be attributed to the short duration of GH hypersecretion as patients 1 and 3 had symptoms for 5 and 6 years respectively (Table 2). Possible explanations for the discrepancy between growth promoting and immunoreactive GH activities include abnormal GH with greater stimulation of the PRL receptor (Nicoll *et al.*

Table 2. Details of patients reported previously who presented with growth hormone excess without somatic features of acromegaly

Duration of symptoms (years)	Tumour size on radiology	Menses	Galactorrhea	GH (μg/l) Basal → Post glucose	Basal PRL (μg/l)	IGF-1 Pre op (U/ml)	Histology	References
4	Macroadenoma with suprasella extension	Normal	Absent	18→ 8	23 (N<15)	7·9 (N<1·2)	Partly acidophilic/partly chromophobe Immunoperoxidase staining: hGH scattered cells Prolactin occasional cells only	Klibanski *et al* (1987)
1/2	Macroadenoma with suprasella extension	Irregular	Present	24→19	19 (N<15)	2·6 (N<1·2)	Similar to patient 1	
1	Macroadenoma with suprasella extension	Irregular	Present	6→ 8	43 (N<15)	–	Similar to patient 1	
1	Macroadenoma	Amenorrhoea	Present	21→16	40 (N<25)	–	Orangeophilic, densely granulated Immunoperoxidase staining hGH numerous cells, prolactin sparse	Tourniaire *et al* (1985)
1	Macroadenoma	Normal, infertility	Present	9·5→9·5	29 (N<25)	–	Partly orangeophilic, partly chromophobe Immunoperoxidase staining: GH numerous cells, prolactin sparsely	
6	Macroadenoma with suprasella extension	Oligomenorrhoea	Present	23→22	40 (N<20)	–	Chromophobe adenoma Immunoperoxidase staining GH-majority of cells, prolactin sparse	Present report
1	Microadenoma	Irregular	Present	38	36 (N<20)	–	No identifiable tumour histologically. Immunoperoxidase staining. increased number of GH and prolactin staining cells	
5	Macroadenoma	Oligomenorrhoea	Present	18→14	20 (N<20)	4·8 (N<1·9)	Mixed acidophylic chromophobe adenoma Immunoperoxidase staining. GH staining cells only	

N = normal range
GH = growth hormone
PRL = prolactin.
IGF = insulin-like growth factor.

1986), or altered GH binding capacity and altered GH receptor activity. In a previous report (Klibanski *et al.* 1987), the GH was 'normal' on sephadex chromatographic examination of the patient's plasma and tumour extract, although a minor structural difference in the GH species has not been excluded. Alternatively, since GH binding proteins in serum (Herington *et al.* 1986; Baumann *et al.* 1986) are known to inhibit binding of GH to tissue receptors (Herington *et al.* 1986) and confine GH to the vascular space (Baumann *et al.* 1987), one explanation for the discrepancy between high immunoreactive and low bioactive GH activity may be the result of abnormal binding of GH to its plasma carrier protein. In patients 1 and 2 serum binding capacity for ^{125}I-GH was normal but was reduced pre-operatively in patient 3. Binding capacity for ^{125}I can be reduced in acromegaly (Herington *et al.* 1986), similar to our patient, but her binding returned to normal after surgery. In patient 3 the binding studies suggest therefore a reduced degree of availability of GH binding sites with the high circulating levels of GH or reduced binding protein concentration (Herington *et al.* 1986).

Finally, the histological features of these tumours is varied, being either typical (Tourniaire *et al.* 1985) or atypical (Klibanski *et al.* 1987). Our first patient is similar to the only other detailed electronmicroscope report (Klibanski *et al.* 1987). Despite positive immunocytochemical cellular staining for GH, ultrastructural features are atypical and do not appear to resemble normal adenomatous GH-secretory cells (Klibanski *et al.* 1987). It is possible therefore that these tumours may represent a distinct morphological entity, which parallels the apparent uniqueness of their clinical presentation.

Conclusion

GH hypersecretion may be responsible for galactorrhoea and menstrual irregularity of many years duration without inducing the somatic features of acromegaly. Although bromocriptine suppresses the mildly elevated PRL levels, it fails to inhibit the galactorrhoea or regularize their menstrual cycles and GH levels remain elevated. Selective surgical removal of the pituitary adenomas returns GH levels to normal with reappearance of regular menstrual cycles. Thus, assessment of GH secretion should be included in the assessment of young women with a pituitary tumour and galactorrhoea and/or menstrual disturbances with only modest elevation of PRL, even in the absence of somatic features of acromegaly.

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Vulval reconstruction by free tissue transfer. Case report

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Case report

The patient was 55 years old and had suffered from lichen sclerosus et atrophicus of the vulva and introitus for 18 years.

Treatment by local applications had been disappointing. She underwent simple vulvectomy in 1973. Further excisions and reconstructions by local flaps were carried out over the period of several years with their eventual involvement by the disease process. Histologically, malignant transformation was never demonstrated. In 1987 she underwent reconstruction of vulva by bilateral gracilis myocutaneous flaps which did not survive. Following this in April 1988 she had a partial reconstruction of the anterior commissure by free lateral arm flap revascularized by anastomosis of the flap vessels to the right femoral vessels. Post-operatively the anastomosis had to be revised and the flap survived. When seen by us in May 1989 the vulva was replaced by a circular cicatrix and the skin around it both externally and internally had become dystrophic (Fig. 1). The small area reconstructed by the lateral arm flap was clinically free from disease The posterior commissure was fissured and intercourse was impossible due to narrowing and pain. There were scars on the medial aspects of both thighs and over the right femoral vessels. The entire perineum was tight and the abnormal skin extended to the anal margin.

In July 1989 the entire clinically affected area of vulva and introitus was excized and resurfaced by a right radial forearm free flap (Song *et al.* 1982; Soutar *et al.* 1983) revascularized by a branch of left femoral artery and a tributary of the femoral vein through interpositional saphenous vein grafts. The diameter of the radial artery and its vena comitans was of the order of 2 mm and anastomosis was carried out with 9/0 and 10/0 nylon sutures using microsurgical technique. The flap, taken from the entire flexor surface of the forearm (Fig. 2), was folded in a U-shape to form the posterior commissure. The vein grafts crossed the upper adductor muscles and the flap became pink immediately (Fig. 3). The medial cutaneous nerve of the forearm, which was included in the flap, was anastomosed to a cutaneous branch of the femoral nerve as the genitofemoral nerve could not be identified. The donor defect on the forearm was grafted with split skin grafts. The entire procedure took 8 h and no anticoagulants were used; 14 h later the flap was noticed to have become blue, cold and congested. On re-exploration the vein grafts were found to be kinked and thrombosed. Both the anastomoses were reconstructed using saphenous vein grafts from the opposite leg. The proximal part of the flap became pink but the distal half showed return of circulation only after being detached. In the postoperative phase the patient received low molecular weight dextran and leeches were used on the distal part of the flap to reduce venous congestion. Most of the flap recovered and 3 days later the distal part of the flap was reattached to the right margin of the defect in the perineum after excision of the terminal 2·5 cm which had become necrotic. After the reconstruction of the anastomoses the patient was nursed in a supine position on a low air loss bed with legs abducted on pillows to avoid kinking of the vein grafts. The adduction of the thighs was allowed gradually after 15 days. Several months later a circular stricture was noticed at the junction of the vaginal mucosa and the flap margin which responded partially to dilatation. She also complained of incontinence of urine. An examination under anaesthesia revealed a patulous external urethral orifice

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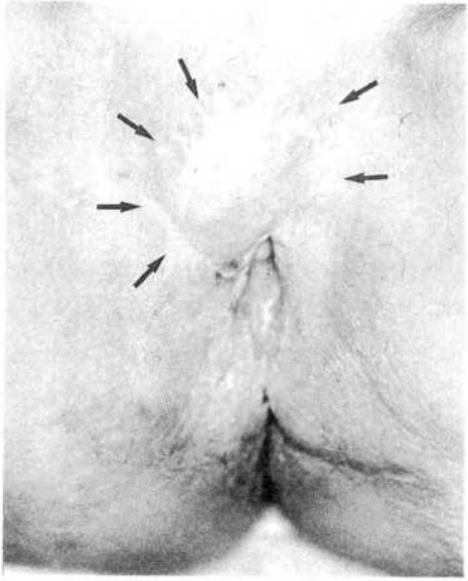

Fig. 1. Preoperative appearance. Note that area resurfaced by lateral arm flap (arrowed) is clinically unaffected.

without scarring or involvement by lichen sclerosus. There was an ulcer at the posterior commissure which on histological examination showed features of lichen sclerosus. The circular stricture was relieved by Z plasties. Six months after the reconstruction the patient has resumed intercourse which had been impossible for several years. She is very pleased with the reconstruction (Fig. 4). She accepts the donor area on the forearm without complaints (Fig. 5). No touch sensation has been noticed in the flap as yet.

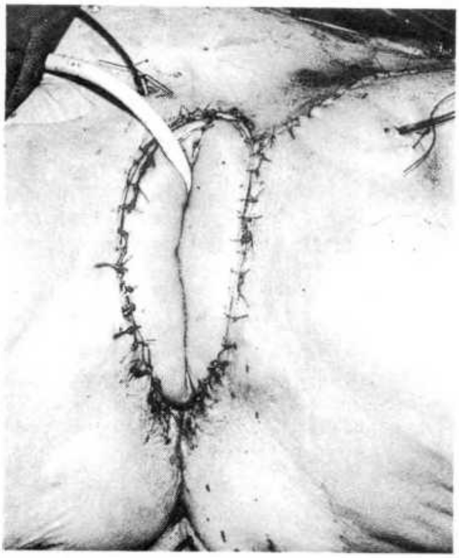

Fig. 3. Immediate post-operative appearance.

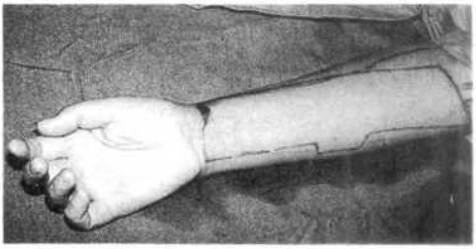

Fig. 2. Flap marked out on the right forearm.

Discussion

Although several regional flaps have been described for reconstruction of defects left by extensive vulvar surgery, a gracilis myocutaneous island flap (McCraw & Massey 1976) is usually the method of choice. However, it is known (Nahai & Mathes 1982; Giordano *et al.* 1990) that skin island on the distal part of this rather narrow muscle often does not perfuse well. Other local and regional flaps available for use have been discussed by other authors (Stern & Lacey 1987). Recently use of bilateral island groin flaps has been reported for vulvar reconstruction (Bertani *et al.* 1990). In our patient reconstruction by gracilis myocutaneous flaps had been attempted previously but did not succeed. Also in contrast to patients undergoing

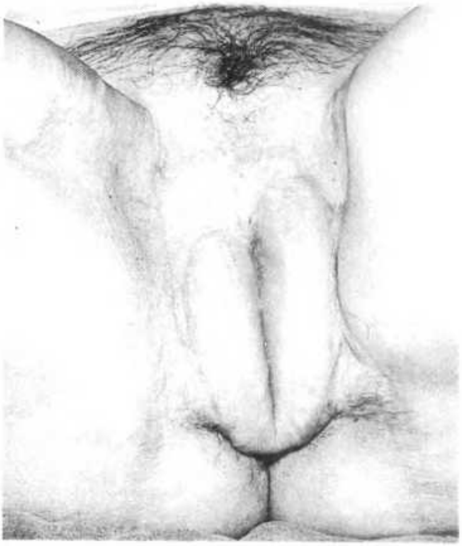

Fig. 4. Appearance six months later. Upper right corner of the flap was lost.

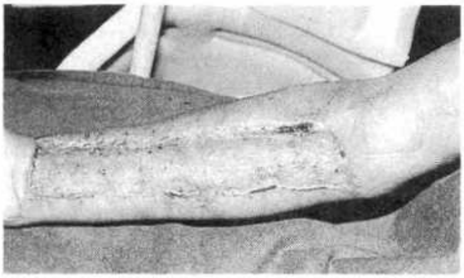

Fig. 5. Appearance of the donor area, three months post-operatively.

radical vulvectomy where large and bulky flaps can be accommodated and desirable. our patient did not require a myocutaneous flap reconstruction as only skin replacement was required. Hence, the tensor fascia lata or rectus abdominis flap was not selected. Since there were no local skin flaps available a thin free flap, i.e. radial forearm flap was used. All methods of reconstruction have their problems and free tissue transfer is no exception. With the experience gained from this patient the following suggestions are made.

1. The choice of donor area depends on the size and depth of the defect. The skin component for the entire vulvar reconstruction needs to be 20 to 25 cm long and 8 to 10 cm wide. Where possible an innervated flap should be chosen and this limited the choice to radial forearm flap in this case. For smaller defects a free flap is probably not needed, but if desired a lateral arm or a posterior calf fasciocutaneous free flap can be used. We have no experience with the latter.

2. Whenever possible the use of vein grafts should be avoided. In both the free flaps used in this patient the vein grafts had to be reconstructed. If used, they should be so placed as not to be affected by the movement at hip joint. A better solution may be to dissect out the inferior epigastric vessels and to reroute them subcutaneously across the mons pubis to make the anastomosis thus avoiding the vein grafts and effects of movement at hip joint. Similar conclusion has been reached by other authors engaged in penile reconstruction (Z. Arnez, personal communication, Harashina *et al.* 1990).

It is not the purpose of this communication to enter into the debate regarding the surgical management of lichen sclerosus et atrophicus. Most workers (Kaufman 1981; Ridley 1986; Scott 1986) advise against surgical excision pointing out the high recurrence rate in the skin grafts. However, little advice is offered about the management of a long suffering patient without evidence of premalignant change. In the latter instance partial vulvectomy has been used (Barker 1962). As far as we know the use of distant flaps in the vulvar reconstruction of patients with lichen sclerosus et atrophicus has not been reported and it will be interesting to monitor the fate of the free flap in this patient.

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A modified contraceptive diaphragm for relief of uretero-vaginal fistula. Case report

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Case report

A 40-year-old woman attended gynaecological outpatients having had urinary frequency and continuous leakage of small amounts of urine from her vagina for 2 weeks. Six weeks earlier she had had a difficult total abdominal hysterectomy for large uterine fibroids.

On examination urine was seen in the vagina and it seemed probable that she had a uretero-vaginal fistula. An intravenous urogram showed a partially obstructed ureter on the right.

Symptom relief was gained by combining a 60mm flat spring contraceptive diaphragm (LRC Products Ltd, London) with a 14 french gauge Foley catheter. The size of diaphragm was assessed by vaginal examination as if its purpose was contraception.

The smallest of cuts was made near the perimeter of the diaphragm, and the balloon of the Foley catheter was removed with an oblique cut. The catheter was inserted gently through the hole from the convex side, being careful not to enlarge the hole further. By pulling gently back on the catheter, a small collar of diaphragm formed on the convex side around the catheter. The obliquely cut end of the catheter was sutured with the point facing towards the rim of the diaphragm using a 2–0 polyglactin (Vicryl) suture. By passing the suture from the convex, outermost, surface through the diaphragm and the cut catheter end, and then reversing a few millimetres away, the suture holes in the diaphragm became covered by the oblique end of the catheter (Fig. 1). It was then possible to form a short collar of diaphragm around the catheter as the suture was tied (Fig. 2). The joins on both surfaces were coated with Opsite moisture vapour permeable spray dressing (Smith and Nephew), and the device left to dry.

The device was placed in the vagina, the concave surface upwards and the catheter entry point anteriorly so that this became the dependant point on standing. The distal end was connected to a urine collection bag which was strapped to her thigh. With the device in place, she was totally dry, odour free, no longer tied to the hospital, and able to walk freely.

A nephrostomy tube was inserted by the urologist and, after the ureteric gap had been bridged by a guidewire, a multi-length pigtail catheter was inserted. The leakage of urine into the vagina ceased after about a week and, subsequently, she has remained dry.

Comment

Uretero-vaginal fistula is a recognized complication of gynaecological surgery, leakage of urine usually beginning from 1 to 4 weeks post-

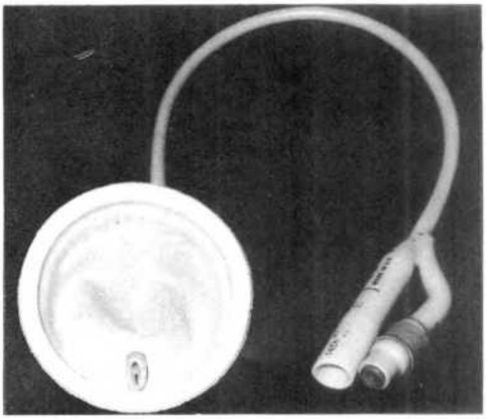

Fig. 1. The modified diaphragm with attached catheter, showing the concave side of the device.

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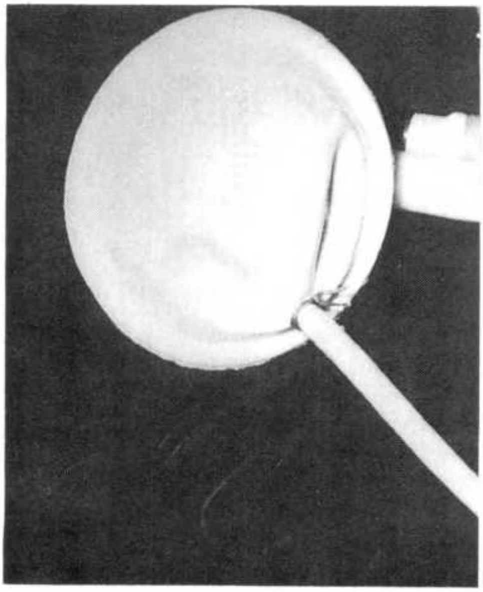

Fig. 2. The insertion of the catheter into the convex side of the device.

operatively (Murphy *et al.* 1982). Immediate relief is usually provided by incontinence pads (Smith 1988), although the use of an intravaginal natural marine sponge inserted into Paul's tubing has been described (Yeates 1959). The device we devised prevents urine loss from the vagina and allows the patient to mobilize with confidence.

Joining the catheter to the diaphragm requires practice, and the device must be tested for leaks before placement. All the details described appear to be necessary if the device is to be satisfactory.

The device is washed and replaced daily. If the device is left in place for prolonged periods, the rubber becomes encrusted with crystals. Our patient had a very tender vagina and insertion was more comfortable if the rim of the diaphragm was lubricated with lignocaine gel.

The joint between catheter and diaphragm fails with time and we suggest a new device each week.

This system was also used successfully by a surgical patient with a similar problem at the same time.

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SHORT COMMUNICATIONS

The clinical presentation of women with human immunodeficiency virus infection

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By February 1990, 81 women with human immunodeficiency virus (HIV infection) were identified in the genitourinary medicine clinics of East Riverside. To investigate the mode of their presentation a retrospective study was performed.

Results

The suspected route of HIV transmission was heterosexual in 43 (53%) of the women, injecting drug use in 34 (42%) and transfusion of contaminated blood products in 4 (5%). Of the heterosexual group 53% were born in Africa, mainly Uganda and the remainder in Europe, North America and Australia. The mode of presentation of the drug users was either directly to the genitourinary clinic or to the drug dependency unit requesting HIV antibody testing or via attendance at the antenatal clinic. However, the presentation of those who acquired the virus heterosexually was far more varied with 18 (41%) of these patients presenting in other ways (Table 1). Overall, 20 (23%) of the patients presented initially to the obstetric and gynaecological departments

Discussion

The importance of sexually transmitted diseases as co-factors for HIV has been reported (Greenblatt *et al.* 1988, Kell *et al* 1990a) in relation to heterosexual transmission. In addition, genital infection may be a presenting complaint in women with HIV infection (Table 1).

Table 1. Non-specific presentations in the heterosexual transmission group

Patient no.	Where presentation occurred	Reason for presentation
1	District General Hospital (DGH)	General malaise and resistant herpes
2	Antenatal clinic	Positive syphilis serology at 26 weeks gestation
3	Gynaecology clinic	Vulval warts
4	DGH	Extreme dyspnoea at 10 weeks gestation
5	Private gynaecologist	'Premarital' check-up
6	DGH	Flu-like illness (delayed seroconversion)
7	Chest clinic	Persistent generalized lymphadenopathy
8	Genito-urinary dept	Herpes contact tracing
9	Gynaecology outpatients	Genital herpes
10	DGH	General malaise
11	Haematology	Tested before blood donation
12	Private gynaecologist	Vaginal discharge
13	Genito-urinary dept	Genital warts
14	DGH	Flu-like illness and general malaise
15	Haematology	Tested at blood donation
16	Post-natal ward	Tested after baby was found to be HIV antibody positive
17	Chest clinic	Persistent generalized lymphadenopathy
18	DGH	General malaise

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We feel that many of the women who contracted the infection heterosexually did not perceive themselves as being at risk and, therefore, did not present for testing even when symptomatic (Glaser *et al.* 1989).

Previously, heterosexual transmission has been confined to 'high risk' groups (Pinching *et al.* 1985) with the implication that these were the only patients who required screening. However, as the infection is now becoming more apparent in those with no obvious risk factor, we recommend that HIV antibody testing should be made more widely available, along with facilities for adequate counselling (Howard *et al* 1989).

The effect of the type of counselling on the uptake of HIV antibody testing may be important (Kell *et al.* 1990b). A study in Philadelphia (Mendez *et al.* 1989) showed that the uptake rate of antenatal HIV antibody testing varied with the type of counselling from 18% to 60%, with the highest uptake rate amongst those counselled without mention of risk factors. Furthermore, there is evidence to suggest that offering HIV antibody testing to 'at risk' women leads to a large proportion of the infected patients not being tested (Kransinski *et al.* 1988).

One of the major problems associated with counselling is the uncertainty as to the effect of HIV on pregnancy outcome and of pregnancy on disease progression. Biggar *et al.* (1989) have shown that HIV antibody positive women exhibit a greater and more sustained fall in CD4 lymphocytes during pregnancy, with less recovery in the post partum period, than seronegative pregnant women, concluding that pregnancy may 'increase the risk of acquired immunodeficiency syndrome'. The results of clinical studies have been unclear. Some studies support this clinical deterioration (Delfraissy *et al.* 1989) whereas others have found no such decline (Bradbeer 1989).

The increasing prevalence of HIV infection in women will pose a major problem to medical personnel. In particular their diversity of presentation. This will inevitably result in problems in both diagnosis and management to the practising obstetrician and gynaecologist, to whom many of the covert presentations may occur.

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Neutrophil activation in small for gestational age pregnancies

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Neutrophils have been implicated in the pathophysiology of vascular damage in man (Harlan 1987). They release a variety of substances which are capable of mediating vascular damage. These include the contents of neutrophil granules such as elastase and other proteases which can destroy the integrity of endothelial cells, vascular basement membranes and the subendothelial matrix (Harlan 1987). In addition, toxic oxygen radicals are released which can result in membrane lipid peroxidation, lysis of endothelial cells and increased vascular permeability and reactivity (Harlan 1987). White cell activation also leads to the synthesis and release of leukotrienes which further increase vascular permeability, induce vasoconstriction and promote further neutrophil activation and adherence (Bray 1983). Neutrophil activation *in-vivo* is reflected by elevated levels of human neutrophil elastase (hNE). We have shown previously that elevated levels of hNE are associated with pregnancy-induced hypertension (PIH) (Greer *et al.* 1989). As the pathological lesion seen in the uteroplacental bed in intrauterine growth retardation (IUGR) is similar to that seen in PIH (Khong *et al.* 1986), the aim of this study was to determine whether neutrophil activation occurs in this disorder by measuring hNE in the peripheral plasma of women with small for gestational age (SGA) fetuses, and comparing this with hNE in uncomplicated pregnancies.

Subjects and methods

Women with clinical evidence of SGA fetuses, confirmed by ultrasound measurements of the fetal abdominal circumference lying <10th centile, were sampled in the third trimester before induction of labour or caesarean section. None of the women was hypertensive, none had had an antepartum haemorrhage and those whose infants had a birthweight >10th centile were excluded before the hNE results were known. Twenty normal women with healthy term pregnancies were studied as a comparison group, they were sampled before elective caesarean section or induction of labour. Peripheral venous blood was obtained from all women after admission for induction of labour or elective caesarean section. None of the women was in labour at the time of sampling, which was performed before the administration of any drugs. The blood was anticoagulated with 3·8% trisodium citrate and centrifuged at 4°C for 10 min within 1 h of sampling. The plasma was then separated and stored at −20° C. Any woman with clinical or laboratory evidence of infection was excluded, as infection will result in increased neutrophil activity. Laboratory exclusions included any woman with a white cell count $>12\times10^9/l$ as this may represent subclinical infection. hNE was measured by radioimmunoassay as described previously (Greer *et al.* 1989), the laboratory did not know the diagnosis. The elastase results were analysed using a modified z-test following log transformation. Age, gestation and birthweight were analysed by Student's *t*-test, and parity and smoking habit were compared by contingency table analysis. The Spearman rank test was used to assess correlation.

Results

The SGA group consisted of 14 women with a mean age of 24·3 (SD 4·9) years and a mean gestation of 40 (SD 2·5) weeks. The primigravid: parous ratio was 7:7 and the smoker:nonsmoker ratio was 5:9. The normal comparison group had a mean age of 25·5 (SD 4·4) years and mean gestation of 39·4 (SD 1·8) weeks. The primigravid:parous ratio was 7:13 and smoker:nonsmoker ratio was 8:12. There was no significant difference between the two groups for any of these variables. All the infants from the normal comparison group weighed > the 10th centile (mean birthweight 3493 g, SD 507). All the infants in the SGA group weighed below the 10th centile weight for gestational age. Six infants were below the 3rd centile, four were

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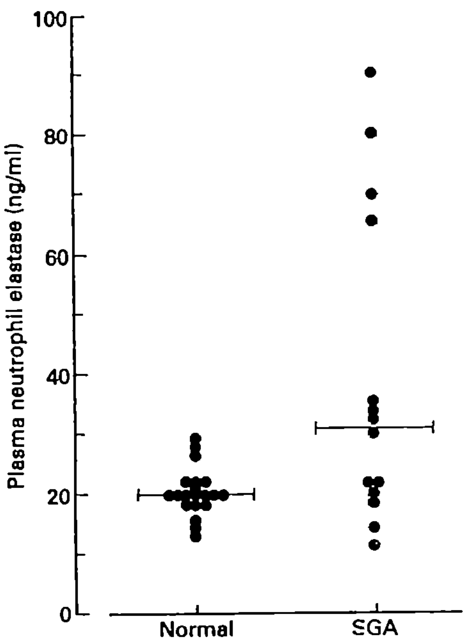

Fig. 1. Maternal plasma human neutrophil elastase in normal pregnancies and pregnancies resulting in small for gestational age (SGA) infants. Cross bars represent the median for each group ($P<0{\cdot}02$)

between the 3rd and 5th centiles, and four were between the 5th and 10th centiles. The mean birthweight in this group was 2319 g (SD 512), which was significantly less than that in the comparison group ($t = 6{\cdot}62$, $P<0{\cdot}001$). The hNE levels were significantly higher in the SGA group than in the comparison group ($z = 2{\cdot}611$, $P<0{\cdot}02$) (Fig. 1). There was no correlation between birthweight and hNE in either the SGA group ($r = 0{\cdot}03$, $P = 0{\cdot}91$) or the normal comparison group ($r = 0{\cdot}14$, $P = 0{\cdot}57$).

Comment

This study is the first to demonstrate that hNE is elevated in pregnancies resulting in SGA infants, suggesting that neutrophil activation-and degranulation occurs in this disorder We have shown previously that neutrophil activation occurs in PIH, this disorder and IUGR share similar pathological changes in the utero-placental bed. Since neutrophil activation occurs in both disorders we would suggest that this may play a role in the vascular damage seen in the placental bed.

In the SGA group there was a wide scatter in the levels of hNE and these did not correlate with birthweight. The SGA group may comprise fetuses that are healthy but constitutionally small, with hNE levels similar to the normal comparison group, and pregnancies with genuine IUGR with elevated levels of hNE suggesting an ongoing disease process. Further work is required to try and categorize SGA infants into these two distinct groups and then determine whether there is a correlation with hNE levels. This may provide a useful marker for those small fetuses which have an underlying placental disease process and therefore are at higher risk than those healthy infants who are genetically destined to be small. In the meantime, however, evidence of neutrophil activation may help advance our understanding of the disease process of IUGR.

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Quantitation of hormone replacement induced withdrawal bleeds

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Unacceptability of withdrawal bleeds induced by cyclical oestrogen-progestogen hormone replacement therapy may lead to discontinuation of treatment. Although it is recognized that women are poor judges of their menstrual blood loss, this easily measured variable has never been objectively estimated in patients taking hormone replacement therapy (Fraser *et al.* 1984). The present study was undertaken to measure withdrawal blood loss.

Subjects and methods

Fifty postmenopausal women, recruited from the Oxford Menopause Clinic, were given 12 cycles of treatment with a new cyclical oestrogen progestogen combination consisting of oestradiol valerate 2 mg continuously and levonorgestrel 75 μg for the last 12 days of each 28 day cycle (Schering Health Care, UK). The women were aged 35–65 years, had a plasma FSH level of >30 IU/l, and had not taken any hormonal preparations for at least 1 month before entry. All had a normal pelvis on clinical examination, and endometrial biopsies at the beginning and end of the study showed no pathology. The days on which bleeding occurred were recorded in daily diaries. Withdrawal bleeds were measured during the 3rd, 6th and 12th treatment cycles using the alkaline haematin method (Hallberg & Nilsson 1964). Withdrawal bleeds were defined as those occurring towards the end of the progestogen phase or early in the following cycle.

Results

Two women did not bleed throughout the study. In the remainder, median blood losses were 26 ml at 3 months (range 1–313 ml, $n = 48$), 23 ml at 6 months (range 2–256 ml, $n = 40$) and 17 ml at 12 months (range 1–106 ml, $n = 29$). Overall 13% of the women we studied had objective 'menorrhagia', with blood losses >80 ml per bleed (Hallberg *et al.* 1966). No women withdrew from the trial as a result of heavy blood loss. Seven women withdrew due to a variety of reasons which included light headedness, feet tingling and weight gain. The median day for onset of bleeding throughout the trial was between days 1 and 3 of the cycle, with a range that extended from day 25 of the preceding cycle to day 6. Overall the median duration of the withdrawal bleeds ranged between 3 and 7 days, with a maximum of 17 days observed in one cycle in one woman. No more than four women bled more than 7 days in any individual cycle thoughout the whole study.

Unexpected bleeding was also noted: this was defined as bleeding separated from the expected withdrawal bleed by at least one day. This occurred in 5% of treatment cycles and lasted on average 1 to 2 days. The longest unexpected bleed was 5 days, but it only happened once.

Discussion

The new combination of oestradiol valerate and levonorgestrel was well tolerated. The blood loss induced by the study formulation is similar to that found in a normal premenopausal population where the median is 35 ml, and the 90th centile is 80 ml (Hallberg *et al.* 1966). Oral contraceptive induced bleeds are lighter than those of normal premenopausal women (Cole *et al.* 1971).

Further work is required to measure withdrawal bleeds induced by other hormone replacement combinations. From the distribution of normal menstrual loss, sample size of 25 women with blood loss measurements after 3 months therapy would provide useful data, although smaller numbers may give a guide (Cole *et al.* 1971; Hallberg *et al.* 1966). Longer term studies would show if withdrawal bleeds change with continued use.

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Certain dates may not provide a reliable estimate of gestational age

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In 16–45% of pregnant women estimation of gestational age from menstrual history has been reported as unreliable due to irregular cycles or inability to remember the last menstrual period (Campbell *et al.* 1985; Hall & Carr-Hill 1985). Ultrasound is used to assess gestational age in these pregnancies and also, commonly, when a difference of ≥7–14 days between ultrasound and menstrual information is noted. In pregnancies where menstrual history seems reliable, or the difference is less, the first day of the last menstrual period (LMP) is used. Use of corroborated evidence has also been advocated (Hall 1990).

There is little information on how women who are able to give a date for their LMP arrive at that date or how accurate such timing is. Certainty of menstrual dates and their agreement with ultrasound measurements was investigated in women attending for routine antenatal booking.

Subjects and results

A total of 315 women with a viable pregnancy attending consecutively at four antenatal booking clinics in our hospital were interviewed by a midwife, either before an ultrasound booking scan (about 50% of them) or immediately afterwards. The exact result of the scan was not revealed until the end of the interview. A questionnaire was used containing 14 questions on age, parity, mentrual cycle patterns, recent hormonal contraception, whether she was sure of her last period and, if she was, how she remembered the date (from diary, by recall or associated life events). Gestation in days by LMP and ultrasound was noted and the difference between these calculated for each woman. Crown-rump length (CRL) (Robinson & Fleming 1975) or biparietal diameter (BPD) measurements (Campbell & Newman 1971) were used, depending on gestational age. These were adjusted for a sound velocity in tissue of 1540 m/s.

The mean age of the women was 27·4 (SD 5·25) years; 130 were primigravida, the other 185 were parous. Overall 239 (76%) said they were sure of the date of their LMP; 14 of these (6%) had noted the last day of the LMP rather than the first for reference. Unsure women numbered 76 (24%).

A total of 150 women (48%) had written down the date of the LMP. A diary was kept by 130 and 127 had recorded the date of their LMP there. Various life events (family, social, work, visits to doctors) were used to aid memory by 56 women. Five relied on cycle regularity, five on when the oral contraceptive pill had been stopped and eight said they had 'a good guess'. Thirty-three (10%) counted back to a likely LMP from the day they had expected menstruation.

Overall, 145 (46%) had regular cycles of 3–7 days bleeding every 28 ± 2 days. Of these, 33 had used the oral contraceptive pill within 3 months before the LMP and 10 had either an abnormally short or prolonged LMP. This left 102 women (32%) in a sub-group with very certain dates. Within this sub-group there were 69 (68%) who had written down the LMP date, but 15 had counted back from the day menstruation should have started. Memory aids were used by 28 women and included social, family or holiday occasions (18), regularity of the cycle (3) and guess-work (7).

Women sure of their LMP were older ($P = 0{\cdot}05$; differences between means) and of lesser parity ($P<0{\cdot}001$) than those who were unsure. In Table 1 gestational age by LMP and ultrasound is shown for different groups of women by how certain they were of the LMP. Gestational age was consistently less by scan than by LMP, with a mean difference from 2·4 days for those with the greatest certainty to 7·5 days for those unsure of the LMP. Individual differences in all 315 women ranged from −66 to +166 days. Among those certain of their dates

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Table 1. Gestational age in days at booking with mean and range of differences from menstrual data (LMP) and ultrasound scan by degree of certainty about dates

		Gestational age (days)		Difference between LMP and scan (days)		
Group	*n*	LMP Mean (SD)	Scan Mean (SD)	d*	SE	Range
Certain of dates	239	97·4 (27·0)	94·8 (26·6)	2·6	1·75	−29 to +54
Certain and 28 ± 2 day cycle	145	97·0 (25·5)	94·6 (25·1)	2·4	2·12	−24 to +37
Very certain dates	102	97·6 (25·3)	95·2 (24·4)	2·4	3·48	−24 to +33

*d = difference between means in days.

There was no significant difference between LMP and scan gestational age by Wilcoxon signed rank test.

the range of differences was smaller (Table 1), but more stringent menstrual criteria produced little additional change. In the group with very certain dates 12 of 102 women had a difference of ≥8 days between gestational age by LMP and scan.

Discussion

The accuracy of certain dates is usually not questioned. Our findings suggested that the date of the LMP, although often written down by the woman, may not be known precisely and may be derived by recall, by reference to recent life events and guessing. In others, cycle irregularity and oral contraceptive use affect the assumed constant relation between LMP and ovulation. In over half the women who said they were certain of the date of their LMP, a detailed history revealed features which could have influenced accuracy of gestational age estimation. This is a higher proportion than described before, but can be ascribed to closer questioning about the LMP and cycle regularity. The range of individual discrepancies was wide and was not substantially bettered by a more detailed menstrual history. Even among those with greatest certainty in their menstrual history it was not possible to predict the one in nine women where there was a difference of more than one week between LMP and ultrasound estimation.

The mean gestational age estimates were not significantly different because of the wide dispersion of gestational age at booking by both methods used. Gestation was on average longer by LMP in all groups. Differences between ultrasound and menstrual dating of pregnancies have been shown previously to affect fetal growth curves and delivery data, shifting the curves horizontally to produce negative skewness both at and past term (Secher *et al.* 1986; Lindgren *et al.* 1988; Persson 1989). Lindgren *et al.* (1988) noted discrepancy between early CRL measurement and menstrual data in 48% of women. Gestational age by LMP exceeded ultrasound estimations by a mean of 3·1 days with wide individual discrepancies, similar to those found in our study. Where available, ultrasound estimation based on well-constructed reference standards may be the better method for assigning gestational age.

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Late recurrence of a congenital diaphragmatic hernia. Case report

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Case report

A 30-year-old woman weighed 58 kg at 16 weeks in her second pregnancy. Her past medical history included the emergency repair of a diaphragmatic hernia as a newborn baby. Her only previous pregnancy had ended in a miscarriage following a laparoscopy.

At 24 weeks gestation she complained of intermittent vomiting, a new symptom as she had had no vomiting in early pregnancy. Urine microscopy revealed 70 white cells but there was no growth on culture. By 27 weeks she was experiencing post prandial pain and the occasional regurgitation of food. An ultrasound examination showed no evidence of gallstones and she was treated conservatively. At 39 weeks gestation she weighed 64.5 kg when she gave birth spontaneously to a healthy infant. At her 6 week post-natal visit she reported that her vomiting had progressed and worsened until she was vomiting after each meal. She now weighed 51 kg, nearly 9 kg less than her pre-pregnancy weight. A barium meal showed that her diaphragmatic hernia had recurred (Fig. 1).

At laparotomy, the fundus of the stomach was in the abdomen with the pylorus drawn up and displaced to the oesophageal hiatus. The rest of the stomach was 'upside down' in the chest (organo-axial volvulus) having herniated through an 8 cm defect at the medial end of the previous repair. Dense adhesions between the stomach, omentum and the large intrathoracic pouch, prevented reduction of the hernia. The abdominal incision was continued as a left thoracotomy along the 7th intercostal space and the diaphragm divided radially. The stomach was mobilized, the defect in the diaphragm closed with interrupted sutures and an anterior gastropexy performed. The chest was drained. Three days later, despite minimal drainage, there was a small pleural effusion present. On the sixth post-operative day she was short of breath and a chest X-ray showed a 'white-out' to the left mid-zone. A diagnostic tap showed thick old blood and a thoracotomy revealed a large clotted haemothorax in the base of the chest which was evacuated.

The patient subsequently made an uneventful recovery and was discharged on the tenth post operative day. Two months later she had regained 7 kg in weight and at 6 months had returned to her normal weight without symptoms of dysphagia or dyspepsia.

Discussion

Vomiting in pregnancy may be a symptom of general disease such as pyelonephritis, duodenal ulcer or hiatus hernia, or may be due to pregnancy itself. Whilst vomiting due to incidental disease can occur at any time during the 40 weeks, nausea and vomiting due to pregnancy usually begin by the 6th and cease by the 12th week.

The commonest and most important type of congenital diaphragmatic hernia is that through the patent pleuroperitoneal canal (Bochdalek) for which surgery is indicated in the neonatal period. The late presentation of this type of diaphragmatic hernia is uncommon. It is a rare complication of pregnancy when its occurrence is presumably related to an increase in intra-abdominal pressure.

The overwhelming majority of diaphragmatic hernias in pregnancy are hiatal. Among 190 000 hospital admissions reviewed by Diddle & Tidrick (1941), only 11 women had non-hiatal diaphragmatic hernias The authors did not specify whether these were associated with trauma or pregnancy and to date only eight examples of congenital diaphragmatic hernia complicating pregnancy have been reported (Reed *et al.* 1987; Kurzel *et al.* 1988; Wolfe & Peterson 1988), and none were recurrent, as occurred in our patient. The hernias present in the third trimester, during labour or in the early post-partum period with abdominal pain, vomiting and shortness of breath. The majority are in primigravidae although there are reports of the problem occurring in a seventh or eighth pregnancy (Diddle & Tidrick 1941; Wolfe & Peterson

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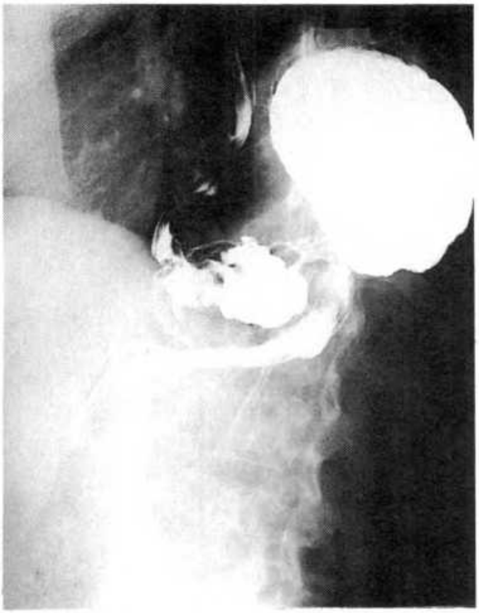

Fig. 1. Lateral view of recurrent diaphragmatic hernia containing incarcerated gastric volvulus.

1988). Non operative management leads to a high fetal and maternal mortality (Osborne & Foster 1953; Kurzel *et al.* 1988), and immediate surgery is recommended (Dave *et al.* 1973; Fardy 1984; Kurzel *et al.* 1988). Simultaneous repair of the hernia at caesarean section is preferable to vaginal delivery, which is to be avoided.

Vomiting is the most frequent symptom of gastric volvulus complicating a para-oesophageal hernia and may present in two ways. An acute onset of severe symptoms suggests significant pathology which leads to early investigation. In contrast an insidious onset may be attributed to the more common causes of vomiting in pregnancy, as our patient illustrates, and investigations delayed. However, failure to attain conventional weight gain ought not to be ignored and in these circumstances vomiting in late pregnancy should to be thoroughly investigated whatever the mode of onset.

In general we favour an abdominal approach when carrying out surgery for para-oesphageal hernias and reflux procedures. Other intra-abdominal pathology can be excluded or dealt with. In this case, however, the lack of a hernial sac was associated with dense vascular intra-thoracic adhesions demanding a thoracotomy for safe mobilization and reduction of the incarcerated stomach. It is of interest that previous recurrent diaphragmatic hernias in pregnancy, one hiatal (Craddock & Hall 1968) and one traumatic (Fardy 1984) were successfully managed by thoracotomy rather than laparotomy, and in this situation the trans-thoracic approach might therefore be more appropriate.

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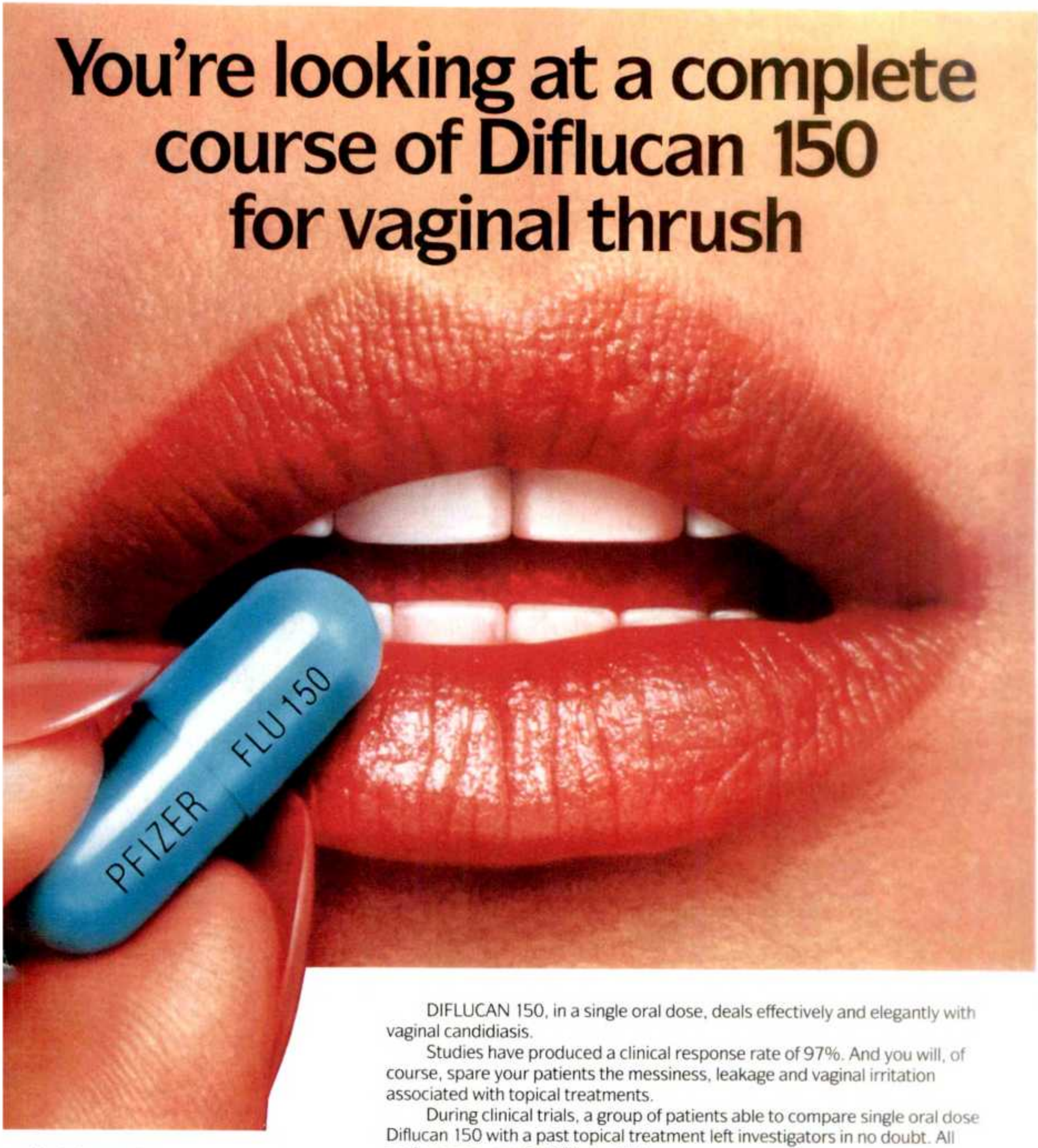

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CORRESPONDENCE

Darier's disease localized to the vulva

Dear Sir,

The report by Barrett *et al* [*Br J Obstet Gynaecol* (1989) **96**, 997–999] contributes a further case to the literature, by now considerable, of acantholytic vulval lesions.

The three patients reported by Duray *et al.* (1983) all presented with a solitary vulval nodule. However, the patients described by Chorzelski *et al.* (1984) and by Coppola & Muscardin (1986) had multiple papular lesions, as did the men with anal canal lesions described by Warkel & Jager (1986) and the one with penile lesions described by Van Der Putte *et al.* (1986). Cooper (1989) has recently described six women with acantholytic lesions presenting with multiple papules (two), or solitary plaques or papules (four), on the labia majora or adjacent skin.

One patient seen by us recently had pruritus vulvae of several years duration; she had some form of radiotherapy in 1981 for this; apparently the skin looked normal at that time. In 1985, when the patient was re-referred still complaining of itching, biopsies showed foci of acantholysis. When seen later in 1985 the appearance was that of mild lichenification and biopsy of the thickened perianal area showed no acantholysis. Whether this implies that the condition was transient or merely not widespread in the ano-genital area in this patient is uncertain.

Common to all these patients is the lack of evidence of Hailey-Hailey disease or Darier's disease elsewhere; they vary, however, in that they may have solitary or multiple lesions or no abnormality visible to the naked eye. Until the true nature of the lesions has been further elucidated it may prove valuable to report examples in some detail and prudent not to beg the question by giving them the title of Hailey-Hailey disease or Darier's disease.

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Transvaginal pulsed Doppler ultrasound assessment of blood flow to the corpus luteum in IVF patients following embryo transfer

Dear Sir,

In a report [*Br J Obstet Gynaecol* (1988) **95**, 1226-1230) our colleagues Baber *et al.* (1988) calculated a resistance index (RI) of Doppler wave forms obtained from the ovaries of women who had undergone in-vitro fertilization or GIFT. They found a highly significant difference in the RI values between the women who achieved pregnancy and those who did not and concluded that this new technique enabled prediction of IVF treatment failure as early as 3 days after embryo transfer.

We continued this work in the same institution using the same methodology from February to July 1988. We recorded 88 ultrasound scans in 56 women of whom 14 became pregnant. In this series of 56 women the mean RI values at 3 and 10 days after embryo transfer were 0·43 and 0·43 in the 14 women who achieved pregnancy and 0·43 and 0·46, respectively, in those who did not become pregnant. There was no significant difference in RI values between the two groups.

The difference between the results of this series and the earlier series reported by Baber *et al.* may be explained by the further experience gained in using this technique and improved equipment sensitivity. Also, we found diastolic flow in all the women within the ovarian capsule, but we did not find diastolic flow in the extra-ovarian portion of the ovarian artery. Baber *et al.* did not find diastolic flow around the corpus luteum in all their women and when they did not, they recorded the RI as 1, this being the RI of the ovarian artery without diastolic flow. This type of signal can always be found at the lateral margin of the ovary.

The situation may be even more complex than we have described here, as we felt that diastolic flow was easier to find in those women who ultimately became pregnant, but this finding is impossible to measure. This may explain why Baber *et al.* found diastolic flow in most patients who became pregnant, but did not always find diastolic flow in those who did not.

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The effect of caput succedaneum on oxygen saturation measurements

Dear Sir,

We were interested in the report by Johnson *et al.* [*Br J Obstet Gynaecol* (1990), **97**, 493–498] that oximetry measurements over caput succedaneum in newborn infants appear to show lower values of oxygen saturation. This finding is of course important for research on intrapartum oximetry where readings are obtained from a probe attached to the fetal scalp.

We attempted to reproduce their data with our method of fetal oximetry (Gardosi *et al.* 1989) which uses, in addition to the plethysmographic signal picked up with the oximeter's photodiode, the ECG signal obtained for fetal heart rate monitoring. The software of the oximeter (CSI 504US) is able to synchronize these two (i.e., optic and electronic) signals, so that weak signals are enhanced and, more importantly, non-synchronized signals are recognized and excluded as they may give falsely low saturation levels (Fig. 1a).

We studied 18 babies with varying degrees of caput shortly after birth. While we agree that it is possible to get some form of oximetry reading in most instances, we were not able to achieve synchronization on significant degrees of caput. In these cases, an acceptable plethysmograph was still obtainable (Fig. 1a) but the rate did not correspond to the true heart rate shown by the ECG. These non-synchronized saturation values had a wide range (34%–97%) and were

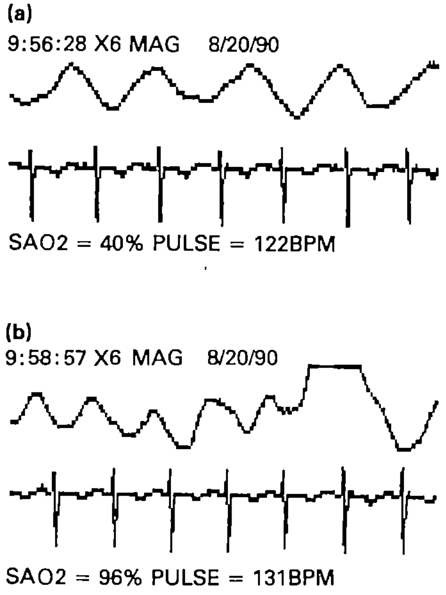

Fig. 1. Simultaneous recording of pulsewaveform and ECG on caput: (a) not synchronized: falsely low saturation reading; (b) synchronized. accurate saturation reading (despite motion artefact).

usually much lower than other, synchronized readings from the same scalp (Fig. 1). The ability to achieve a reliable, synchronized reading was inversely related to the degree of caput present; in many instances, placing the probe just next to caput allowed synchronization and the readings became accurate.

We suggest that the findings reported by Johnson *et al.* demonstrate the need to exclude artefact. Pulse oximetry is meant to reflect arterial saturation levels, but over caput a regular plethysmograph may also reflect pulsations that are venous or transmitted through oedematous tissue. Synchronizing the readings to the true heart rate from the ECG may avoid this problem.

The clinical relevance of oximetry over caput is limited, as the latter usually develops after there is sufficient cervical dilatation to be able to avoid placing the probe onto it. If caput develops later underneath the probe, our system will show a loss of signal synchronization and the oxygen saturation readings are rejected as unreliable, indicating a need to reposition the probe.

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Commentary. Detrusor instability—current management

Dear Sir,

I enjoyed Linda Cardozo's commentary on current management of detrusor instability (*Br J Obstet Gynaecol* (1990) **97**, 463–466]. However, she neglected to mention one form of therapy which might truly be described as 'current management'—namely electrical stimulation of the pelvic floor muscles. Plevnik *et al.* (1989) have published a recent review.

The technique involves the insertion of either vaginal or anal electrodes (or both) through which a pulsed current is passed. The treatment is carried out over a period of several months using low strength stimuli or over a much shorter period using high strength stimuli at the patient's maximum level of tolerance. The mode of action is uncertain, however, Eriksen *et al.* (1989) state that, in idiopathic detrusor instability, there is lasting reinforcement of the intrinsic inhibitory mechanism within the detrusor by normalising a disturbed balance between cholinergic and beta-adrenergic neurotransmission.

The omission of electrical stimulation from Cardozo's commentary reflects the fact that, although this therapy is widely used overseas, it has not yet been established in this country. We are presently assessing acceptability and efficacy in women presenting to our department with idiopathic detrusor instability because it appears to offer significant help in a condition which is notoriously difficult to treat effectively.

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Author's reply

Dear Sir,

Dr Hosker's comments are quite correct. Maximum electrical stimulation has never gained popularity as a method of treatment for detrusor instability in the United Kingdom despite the fact that it is widely used in Scandinavia and also in Yugoslavia with good reported rates of improvement. I suspect that one of the reasons why it has not been used is that this type of treatment has been advocated in the management of both detrusor instability and genuine stress incontinence and it is difficult to understand how it can work in both conditions when the underlying pathophysiology is so different. In addition there has been inadequate asessment of maximum electrical stimulation as it is difficult to provide a control group for comparison. It is with this in mind that we too are conducting a study to compare maximum electrical stimulation with drug therapy, which is the most widely employed method of treatment for idiopathic detrusor instability at present. We look forward to comparing our results with those from Manchester.

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Use of Gynocheck endometrial tissue sampler in infertility

Dear Sir,

We were interested to read the short communication by Smith [*Br J Obstet Gynaecol* (1990) **97**, 454–455], in particular that the procedure was tolerated very poorly.

We performed a prospective trial involving 44 consecutive women attending the gynaecological clinic for the first time with abnormal vaginal bleeding. As a primary procedure either Gynocheck endometrial tissue sampling was performed or the patient was listed for a dilatation and curettage (D&C). The reasons for a D&C were a need for examination under anaesthesia or an associated procedure needing an anaesthetic (laparoscopy or cervical cautery), bleeding associated with abortion, an enlarged uterus, the possibility of endometrial polyps and a failed Gynocheck procedure. Of the 44 women 27 (61%) were initially investigated by a Gynocheck (mean age 45 years) and 17 (39%) had a D&C, their mean age was 50 years. Of the 27 women who had a Gynocheck procedure (and were therefore spared a D&C), the operator found the procedure easy in 25 (93%) and difficult in the other two. The procedure failed in one woman who was nulliparous. The women assessed the Gynocheck procedure by completing a questionnaire. On a visual analogue pain scale 21 of the 27 (78%) said they experienced mild pain (score 0–4) and only 2 (7%) experienced severe pain (score 7–10). These two women did not require analgesia and were returned home from the clinic. The pain experienced appears to be short lived. In comparing the procedure to that of having a cervical smear taken, 8 (30%) found the procedure similar and 19 (70%) found it to be worse. This is not surprising as the cervical canal is penetrated by the Gynocheck instrument. Only four women had had a coil fitted previously and they all found the Gynocheck procedure similar.

We have now performed over 200 Gynocheck procedures, including nulliparous women and in the investigation of infertility. We find that Gynocheck is acceptable to both patient and operator. We have not had any complications, analgesia has not been used and no patient has required hospital admission.

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Autoimmune ovarian failure with elevated serum levels of uteinizing hormone and enlarged ovaries

Dear Sir,

In the discussion of their intriguing case report, Burrell *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 362–364] suggested that the ovary was still capable of producing factors that stimulate stromal growth. There is an alternative explanation that would link directly the autoimmune condition and the ovarian findings.

There is accumulating evidence to suggest that the ovary is influenced by insulin (Poretsky & Kalin, 1987) and that the polycystic ovary is the result of elevated insulin concentrations (Diamond *et al.* 1988). In most cases the fundamental lesion appears to be an inherited defect of the insulin receptor or the postreceptor mechanism which renders it resistant to insulin. In order to maintain glucose homeostasis, insulin levels rise. In a small proportion of patients insulin resistance is acquired as a result of development of antibodies to the insulin receptor (Taylor *et al.* 1982; Kellett *et al.* 1988). It would be interesting to know if the patient described by Burrell *et al.* had hyperinsulinaemia and antibodies directed against the insulin receptor as well as anti-ovarian auto-antibodies. This is not simply a matter of academic interest Insulin resistance is associated with an increased risk of non-insulin-dependent diabetes mellitus (Gerich, 1988), hyperlipidaemia (Laws *et al.* 1989), and hypertension (Ferrannini *et al.* 1987), all independently of obesity. Moreover, the gynaecological complications of insulin-dependent ovarian dysfunction do not finish with the menopause. The stromal tissues remain hyperplastic (Nagamani *et al.* 1988), as in this patient, and therefore hyperactive endocrinologically. As a consequence, there is an increased risk of endometrial neoplasia, hence the association between endometrial carcinoma, diabetes mellitus and hypertension.

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Authors' reply

Dear Sir,

As Dr Fox comments, recent studies have suggested links between ovarian function and insulin, particularly in relation to polycystic ovaries. However, the relationships are not clearly defined and the underlying mechanisms remain 'largely hypothetical' (Poretsky & Kalin 1987). We would therefore be cautious about drawing conclusions regarding elevated insulin concentrations and polycystic ovaries, particularly when the diagnosis of polycystic ovaries also remains controversial. If we agreed that there were an 'insulin-dependent ovarian dysfunction', the postmenopausal pathology would presumably be, that hyperplastic stroma produces excess androgens which are converted to oestrogens peripherally and consequently lead to endometrial hyperplasia. In the case we reported, androgen concentrations were normal and the oestrogen concentrations were low. Although we did not determine the insulin status, we think that it is unlikely that elevated insulin concentrations are the primary pathology in this patient.

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BOOK REVIEWS

The Greek Way of Life by Robert Garland. Duckworths, London, 1990. 376 pages with 45 illustrations, £24

This fascinating book discusses the superstitions, medical beliefs and attitudes of the Ancient Greeks relating to the different stages of human life at a time when scientific and rational thought began to replace superstition in medicine.

The debate surrounding termination of pregnancy was similar to that of today. The Pythagoreans believed that life began at conception and were strongly against termination whereas Aristotle argued that termination of pregnancy when medically indicated should be permitted up until the fetus becomes capable of perception, though we do not know at what gestation this was thought to occur. The Spartans on the other hand practised 'exposure'. The newborn did not have the right of life until several days after delivery so that soon after delivery a child that did not appear healthy would be exposed by the mountain side and be left to the will of the gods. The dangers of termination of pregnancy were recognized by Hippocrates who stated that abortion can result in inflammation of the womb which can lead to ill health and sterility.

Early superstition dictated that childnessness was divine retribution for offences against the gods. However, by the beginning of the fifth century BC scientific explanations for infertility, which apportioned equal responsibility to both males and females, began to appear in medical writings. The Hippocratic corpus discusses a number of tests for the investigation of the infertile couple. In order to assess the patency of the 'female passages' it was recommended that a woman should be covered with cloaks and incense burned beneath her. If the smell of the incense appeared to pass right through the body into her mouth and nostrils then the passages were patent and she was not sterile. Aristotle observed that fat women are less fertile than those that are thin but Hippocrates warned that excessively thin women have a tendency to miscarry. Infertile men were given the same advice as today in that they were encouraged to avoid hot baths and not to consume excess alcohol. Pregnant women were instructed to take exercise and avoid alcohol, advice that is still given today.

Deliveries were conducted by midwives and physicians did not attend routine deliveries and thus encountered childbirth only in its pathological aspects. The qualifications required of a midwife were that she be moderately intelligent, respectable, robust with long slim fingers and short nails. She should be free from superstition and literate in order to comprehend her art through theory. These were better qualifications than those required by the Bishops Licence in 18th century England.

It is unlikely that the classical Greeks were aware of the infective nature of certain diseases yet their writings frequently stress the need for cleanliness during childbirth. Furthermore the practice of forbidding a midwife from offering her services elsewhere for a number of days following a delivery would have helped reduce the risk of post-partum infection.

Long before the discovery of prostaglandins Aristotle noted that women who have intercourse with their husbands before giving birth do so more quickly and a variety of sources referred to a drug called 'Okutokion' which was used to accelerate delivery. A number of positions were utilized for childbirth. The birthing stool was used as was the squatting position, though women also gave birth on a bed or couch (Kline)—from which we derive the word 'clinical'. Aristotle advocated a form of breathing exercises to relieve the pain of contractions. There is no evidence to indicate that the Greeks used the forceps to deliver a live child though instruments were described to perform embryotomy following intrauterine death.

A variety of concoctions were inserted into the vagina which may have been effective spermicides for contraception however the rhythm method was unlikely to have been successful as the Ancient Greeks believed that women were most likely to conceive when they were menstruating.

In early adulthood women were considered the subordinates of men. The place of the married woman was inside the home and her principle duties were child rearing, supervising the slaves and running the household. Classical Greek writers stated that the menopause generally occurred when a woman was in her fortieth year though some women continued to menstruate up to the age of fifty. The cessation of menstruation was known to be associated with physical as well as psychological changes that places the woman at grave risk and long before the days of hormone replacement therapy Greek physicians described the use of suppositories to avoid the abrupt cessation of menstrual flow.

Following the menopause a woman would enjoy greater freedom and independence, and she would be permitted to appear in public unattended. The author suggests that this increase in independence may not have been due to an enhanced status but would be a manifestation of their diminished value. As women past the menopause were no longer capable of supplying heirs there was not the same need to ensure their protection. Few women reached old age and the responsibility for looking after the old rested with the family. Only the elderly whose heirs had died in battle received state support.

This stimulating book is clearly the result of much detailed research. It is well written and deserves to be a success. It should be of great interest to gynaecologists because of the numerous references to the social and medical attitudes to women's health which in spite of great scientific advances have, in some regards, changed very little since classical times.

Michael Savvas

Prenatal Care. Reaching Mother, Reaching Infants edited by Sarah S. Brown for the Institute of Medicine. National Academy Press, Washington, D.C., 1988, 254 pages with figures and tables, £17.15

The proportion of American women receiving adequate 'prenatal' (ante natal) care improved during the 1970s but declined in the early '80s to a level which is incredible in a rich country in which so much money is being spent on health care. In 1985, as many as 8% of pregnant women had inadequate care and only 68% were adequately cared for. Of course, the evaluation of the content and cost effectiveness of ante natal care presents major problems which are (quite appropriately, in my view) sidestepped by the Institute of Medicine Committee which generated this hard-hitting and well-focused report. They eschew also the use of outcome measures such as low birth weight, short gestation and mortality, and deliniate the size of the problem using birth certificate data on when in pregnancy care started and how frequent visits were—a good example of when the quantifiable and the important are the same thing.

Barriers to care are explored in detail using published and unpublished sources. Financial barriers are frequently insurmountable for poor, young single or uninsured women: Medicaid provision is often not advertised and difficult to apply for; many poor women are not eligible, but in any event the re-imbursement is insufficient to pay for care by private obstetricians. Clinic capacity is uneven and cannot cope with all women needing care. Delivery care is funded separately from ante natal care and pre-admission deposits may be required. There are also personal and cultural disincentives to utilization of care by some women. One of the well argued conclusions of the book is that outreach, searching for women not receiving care, is not worthwhile as long as financial barriers persist and clinics are unable to accommodate their current clientele. Very many successful initiatives are described and commended, however, and the book is far from being negative in tone. The bodies who funded the study got excellent value for money, and the book will be of great interest to health care providers and organisers and to politicians. I hope it will be read by the 'radical' right in Britain who are flirting with private insurance as a method of financing health care. The fractured and fragment system described here could result.

Marion H. Hall

Gift: From Basic to Clinics (Serono Symposia Publications, Raven Press, Volume 63) edited by G. L. Capitanio, R. H. Asch, L. De Cecco & S. Croce. Raven Press, New York, N.Y., 1990, 474 pages with figures and tables, $115.50

The original meeting, and now this publication, have brought together many of the top experts in the field of assisted reproduction. The book combines the results of the latest research and also up-to-date reviews within this area of reproductive medicine. Despite having almost 100 contributing authors the book is in general, clearly written and achieves its aims.

The first two papers outline the impact the introduction of the GIFT technique has had on the treatment of some aspects of infertility. The next section contains papers outlining the results of recent research into aspects of gamete and embryo physiology, fertilization and implantation. Some of the topics covered in this section include: follicular recruitment, growth factors in follicular fluid, gamete quality and control of the corpus luteum.

The second half of the book, containing 17 papers, describes some of the most recent developments in the clinical field, with particular attention being paid to the GIFT procedure. The clinical papers begin with an authoritative review of the indications, results, problems and perspectives of using GIFT, by one of the foremost workers in this field, R. H. Asch. The review is supported by ample data from the author's own work and that of others.

The clinical papers that follow cover many new aspects and refinements associated with this area of reproductive medicine. Inevitably, as the editors admit in their preface, although the work was up to date at the time of printing, some is out of date by the time it is read. Despite this I feel the book constitutes a significant collection of important biological and clinical data, well presented, and will form a useful reference source for those who work in reproductive medicine.

Peter McFaul

A Clinical Guide for the Care of Older Women by Richard L. Byyny & Leon Sperofff Williams & Wilkins, Baltimore, Hong Kong, London, 1990, 318 pages with figures and tables, £43.50

It gives me great pleasure to review the above book which I received with great trepidation. It is very unusual for a physician and an obstetrician/gynaecologist to work together, even more rare for them to write a book together, but I am happy to say that the result of their union is a great success.

I suspect from this publication that the United States is much more advanced in their approach to the preventive aspects of gynaecology than Great Britain. We have much to learn.

As well as very well researched chapters on the urinary and pelvic floor, the external genitalia and the breast, there are equally informative chapters on endocrine problems, hypertension, pain, the biology of ageing, successful ageing, the sexuality of old age and obesity as well as many others.

All chapters are easy to reach and end with a comprehensive bibliography which include references to English research. It is obvious that great care has been taken to make reading equally informative to the gynaecologist and the practising physician. As a physician, who specializes in diseases of old age, dare I suggest to a gynaecological audience that with a rapidly ageing United Kingdom population, it is about time we took a more aggressive approach to the care of older women. I would recommend this publication to all practising gynaecologists. It would certainly be a very successful addition to the departmental library.

J. E. Morris

Books received some of which will be reviewed at a later date

Fetal Autonomy and Adaptation edited by G. S. Dawes, F. Borruto, A. Zacutti & A. Zacutti Jr. John Wiley & Sons, Chichester, 1990, 196 pages with figures and tables £35.00

Infection in the Newborn. Perinatal Practice Volume 6, edited by J. de Louvois & D. Harvey. John Wiley & Sons, Chichester, 1990, 164 pages with figures and tables £39.50

Introduction to Clinical Gynaecological Urology by John R. Sutherst, Malcolm I. Frazer, David H. Richmond & Bernard H. Haylen. Butterworth-Heinemann, London, 1990, 170 pages with figures and tables £19.95

Essential Medical Genetics Third Edition by J. M. Connor & M. A. Ferguson-Smith. Blackwell Scientific Publications, Oxford, London, Edinburgh, 1991, 259 pages fully illustrated, paperback £12.95

Infectious Diseases. Prophylaxis & Chemotherapy by J. Schneider, J. Hughes & A. Henderson. Appleton & Lange, Australia, London, 1990, 490 pages £54.95

Drugs in Pregnancy. A Reference Guide to Fetal and Neonatal Risk Third Edition by Gerald G. Briggs, Roger K. Freeman & Sumner J. Yaffe.

Williams & Wilkins, Baltimore, 1990, 732 pages £45.00

Baillière's Clinical Obstetrics and Gynaecology: Volume 4, No 3, Induction of Ovulation edited by P. G. Crosignani. Baillière Tindall, London, Philadelphia, Sydney, 1990, 419–654 pages, single issue £22.50. Annual subscription £49.00

Bioengineering in Reproductive Medicine by Sujoy K. Gua. CRC Press, Boca Raton, Ann Arbor, Boston, 1990, 305 pages with figures and tables £136.00

CRC Handbook of the Laboratory Diagnosis and Treatment of Infertility edited by Brooks A. Keel & Bobby W. Webster. CRC Press, Boca Raton, 1990, 431 pages £78.00

Legal Principles and Practice in Obstetstrics and Gynecology Volume II edited by Max Borten and Emanuel A. Friedman, Year Book Medical Publishers Inc. Chicago, London, Boca Raton, 1990, 364 pages, no price given.

The Baby Machine. Reproductive Technology and the Commercialisation of Motherhood edited by Jocelynne A. Scutt, Green Print, London, 1990, 342 pages £8.95

Syllabus of Gynecologic Pathology with Clinical Correlations by Tung Van Dinh. University of Texas Press, Austin, 1990, 170 pages with illustrations $15.95

Year Book of Obstetrics and Gynecology 1990 edited by D. R. Mishell, T. H. Kirschbaum & C. Paul Morrow. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1990, 520 pages with figures and tables £44.00

Proceedings and Symposiums

Progress in Clinical and Biological Research Volume 358. Treatment of Post Surgical Adhesions. Proceedings of the First International Symposium for the Treatment of Post Surgical Adhesions held in Phoenix, September 1989, edited by Gere S. DiZerega, L. Russell Malinak, Michael P. Diamond & Cary B. Linsky. John Wiley & Sons Inc., New York, Chichester, Brisbane, $64.95

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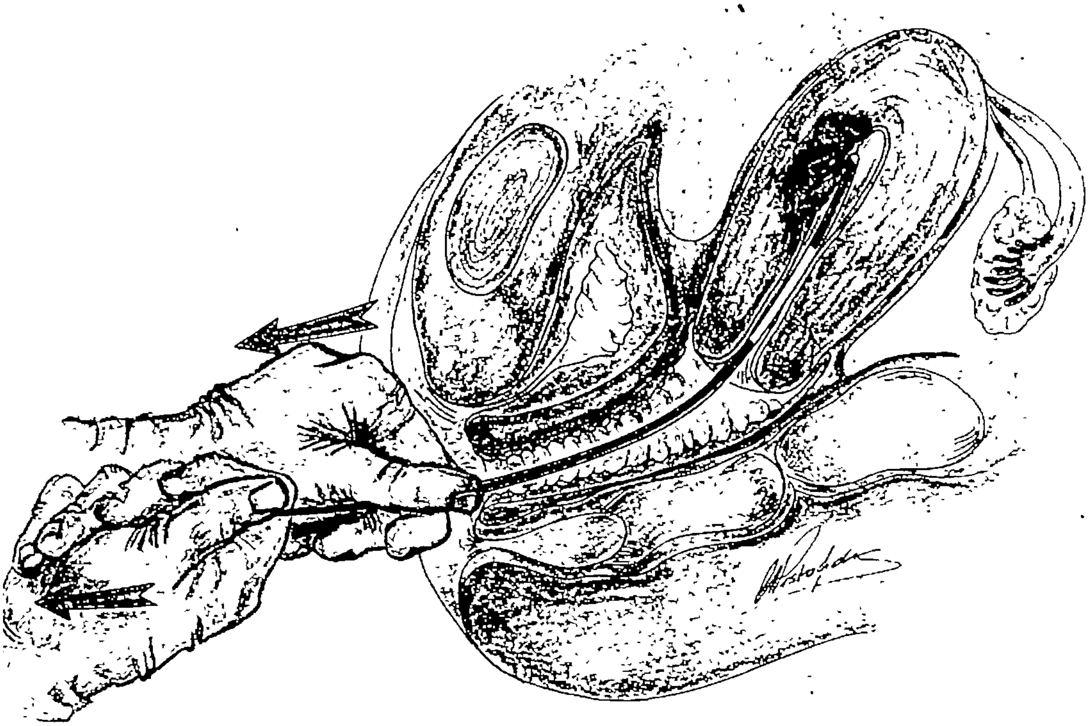

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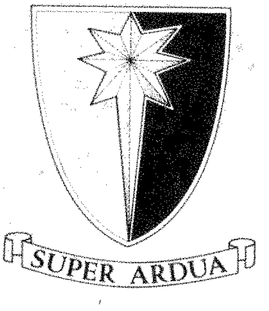
Edited by David B. Paintin



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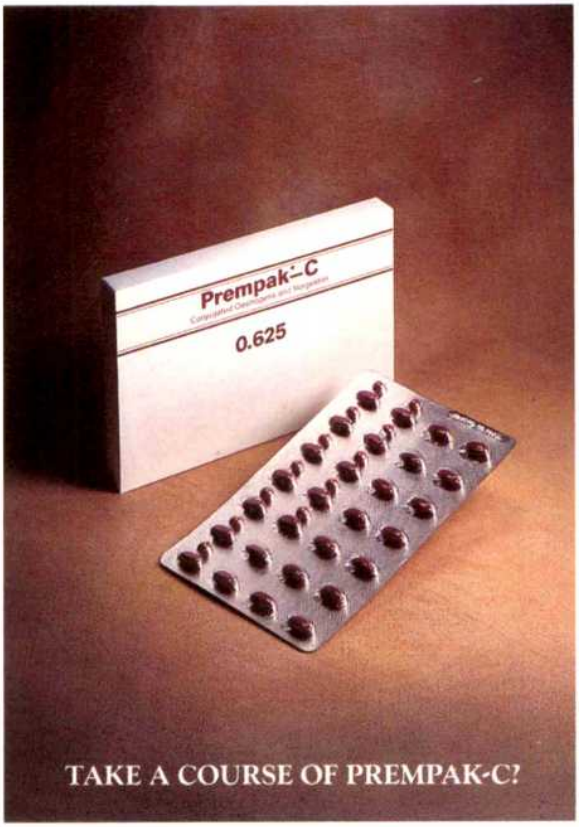

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Manuscripts are subjected to peer review in relation to both the scientific and the statistical content. As far as possible the scientific referees are unaware of the authorship or the department of origin of the work

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Three copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins. To facilitate blind refereeing, the names of the author(s), their appointment(s) and their department(s) should be given on a separate front sheet and any acknowledgments on a separate back sheet. As far as possible, authors should avoid identifying themselves or their department in the text, but such identification is inevitable in some types of paper. Authors are advised to keep a copy of all manuscripts, as no responsibility can be accepted for loss.

Reports of original work should usually be arranged in the conventional order of summary or abstract, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used; the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables Structured abstracts of up to 200 words are preferred to a summary. Where appropriate, the headings should be: Objective; Design; Setting; Subjects, Interventions; Main outcome measures; Results, Conclusions.

Case reports and short communications do not require a summary or introduction. Short communications should not exceed 600 words and contain no more than one table or figure.

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Coloured illustrations are used sparingly when these appreciably improve clarity.

Figures should be marked on the back (lightly in pencil) only with the name of the paper, the figure number and to indicate the top. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs. Original X-ray films should not be sent—glossy prints must be submitted.

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself.

Unless written permission for publication from the patient, or the parent or guardian is submitted, the identity of patients in illustrations should be completely concealed by restricting the field to the area of interest or by obscuring the face.

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors. Standard abbreviations, without punctuation, are used. *Units, Symbols and Abbreviations* (1988) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis.

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Authors should describe clearly the design of their investigation and the source of the data. All statistical methods should be specified so that it is clear which was used where Papers omitting this information may be returned without review The basic principle to follow is to supply sufficient information about the design and methods of analysis to allow the research to be repeated by someone else.

The journal has published check lists to guide contributors preparing accounts of certain types of research. These appeared in 1989 (Vol 96). Bracken M. B., Reporting observational studies, 383–388; Wald N. & Cuckle H., Reporting the assessment of screening and diagnostic tests, 389–396; Grant A., Reporting controlled trials, 397–400.

Some points of detail to note are:

(1) It is not acceptable to present the results of a statistical analysis solely by a *P* value—actual results such as means or proportions should always be given, along with the test statistic.

(2) The use of confidence intervals is encouraged.

(3) The symbol ± should not be used when presenting SE or SD Presentation such as 'the mean . was 14·2 (SD 3·2) mg' is preferred.

(4) When paired comparisons are made it is desirable to indicate the variability of within-pair differences.

(5) Unusual methods of analysis should be described and/or referenced

Authors are referred to the general statistical guidelines of Altman *et al.* (1983) for advice about the presentation and interpretation of the statistical aspects of their research.

Altman, D. G., Gore, S M., Gardner, M. J. & Pocock, S. J. (1983) Statistical guidelines for contributors to medical journals. *Br Med J* **286**, 1489–1493

Human experiments

Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

References

In the text, use the name of the author(s) followed by their date of publication, where there are two authors use the form: Smith & Brown 1972; where there are more than two authors use Robinson *et al.* 1979

Arrange the list of authors quoted at the end of the text in alphabetical order set out as follows:

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References to 'personal communications' and 'unpublished work' may be quoted in the text but should not be included in the references. Examples of the style to be used are given below:

Trudinger B. J., Lewis P J. & Petit B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432-436.

Hytten F. E. & Leitch I. (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26.

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COMMENTARIES

Medical education

'The essence of medical education,' said the great Osler, 'lies in the communication of enthusiasm to the medical student.' It should not be difficult to achieve this aim in our discipline. The students generally find obstetrics exciting and gynaecology interesting—after a period of severe stress while they master the unique histories and clinical examinations involved. Students enjoy dealing with young patients, they respond to the rumbustious 24-hour life of the labour ward and they will carry to their graves the memories of their own first delivery, the subsequent 'phone call to their parents, and the realization that they are, after all, going to be of some practical use to society. Given this flying start, how should we locate, design and execute the undergraduate courses of our medical schools in order that our future general practitioners will care for women with efficiency and sensitivity, and in order that some of the brightest and the best students will have their interest in obstetrics and gynaecology catalysed into a career decision?

Encouraged by the education committee of the General Medical Council, a significant advance in thinking about undergraduate education is taking place in United Kingdom medical schools with the long overdue realization that the students are there, not to be trained, but to be educated. The advent of structured postgraduate training in all major disciplines and the growing acceptance of continuing medical education thereafter has, or should have, set the medical schools free. They, and their constituent departments can now, if they wish, shed the strait-jacket of trying to train mini-specialists in each discipline, and concentrate on producing a graduate intellectually and organizationally prepared to benefit from the obligatory postgraduate training. Old habits die hard, however, and the task of replacing training with education will be a slow, hard evolution rather than a rapid, easy perestroika.

This potential freedom to educate should allow advantage to be taken of new understandings in the field of tertiary educational psychology, concerning how students actually learn. Such knowledge may have a severely practical use in the design of course structure and content. For example, the clear demonstration by Ramsden & Entwistle (1981) that course overloading—a common medical misdemeanour—results in superficial and unsatisfactory learning, should encourage departments to police the course content so that insertions of the new are rigorously balanced by deletions of the old. Equally, the significant numerical decline in academic teaching staff during the early 1980s—although now stabilizing—has meant that, given a constant number of medical students, certain consequences must follow. Either teaching standards are allowed to fall, or academics must spend less time on research and clinical work to protect the teaching component or, most acceptably, more efficient use must be made of the teaching time available (Hibbard *et al.* 1985). Senior students themselves have found a voice and are, quite rightly, reminding their teachers that they are contemporary with qualified lawyers, engineers and scientists and are less than enamoured of didactic teaching methods literally unchanged for decades and which treat them like bygone schoolchildren.

The General Medical Council (GMC 1980) has a statutory duty to monitor the performance of UK medical schools, but the remit of its education committee contains two serious restrictions. First, it is concerned largely with the output rather than the process of medical education, its inspectors 'sitting in' on final examination sessions, the objectivity of which are often less than satisfactory. Second, the committee's attention is directed more at the floor rather than at the ceiling. It is concerned, rightly, that the output of the schools does not fall below an acceptable standard, but has no power to reward excellence or to encourage innovation. It is thus left for individual academic departments to generate, in isolation, their individual approaches to the teaching of our discipline and hence, the paper by Biggs and colleagues in this issue is both timely and instructive.

With regard to the siting of our discipline in the overall medical curriculum, the majority of schools set the clinical course in the fourth or penultimate year. If a rotating block system is in operation—and this is the rule—the students may begin fourth year with obstetrics/gynaecology, having only had the variable and often unsatisfactory clinical exposure of third year to guide them. For this reason there is much to be said for obstetrics/gynaecology occupying, with paediatrics, a block in the final year. The gynaecological examination of breast and pelvis and the paediatric examination of the child and newborn infant have strong emotional components and should be in the hands of students who are already as clinically experienced as possible. The converse may lead to a failure to gain self-confidence in these procedures which may in turn result in a lifelong apprehension or aversion, which may be harmful to patients. There can be few gynaecological staff who have not been rendered hypertensive by the refusal of newly-qualified medical or surgical house officers to perform a pelvic examination even when clearly indicated, the reason usually advanced being a fear of hurting the patient. The real reason is, of course, that they have not been properly taught.

The process of undergraduate education in reproductive medicine begins in the preclinical years and is wildly various. This variability is international, and has surfaced repeatedly at workshops on undergraduate obstetrics and gynaecology, both in the UK (Purdie 1987) and in the USA (Commings & Waxman 1988). There is little doubt, however, that the later teaching of clinical obstetrics and gynaecology gets off to a flying start if it is received by a student with a sound knowledge of pelvic anatomy and reproductive physiology. Conversely, a sound ignorance of the sciences basic to our discipline inevitably means that the symptoms and signs of common conditions have to be learned *in vacuo* rather than being perceived as the necessary and logical results of pathophysiology. It is interesting that Biggs *et al.* in their review of undergraduate teaching, report that in most of our schools, the basic reproductive science training is still located in the second year of the course. Given the packed curriculum and the passage of 2 or even 3 years, it can be hardly surprising if the basic science floor has to be relaid piecemeal at the start of the clinical course. Hence, the initiative of such schools as Southampton where the clinical department is intimately involved in the design and content of basic science teaching, is to be applauded.

With regard to the clinical course itself, the core objectives of teaching can be broadly stated. A new graduate should leave the medical school with the ability to take a deft, thorough and courteous history from any woman of any age, pregnant or not. The graduate should also be capable of performing whatever gynaecological clinical examination is indicated by that history and of doing it in a careful and respectful manner. He or she should have sufficient knowledge to determine if the clinical condition revealed by history and examination may be managed personally or by specialist referral. Finally, our graduate should be alert to any ethical issue posed by that management and should be able to discuss such an issue constructively and in lucid English.

With regard to the question of instruction in pelvic examination, it is clear that despite occasional crises, common sense rules the day. The students have to learn, patients have to be respected, and the live model approach, so successfully developed in the United States (Beckmann 1988), has not been replicated here. Patients should simply be told the truth. They should be told that the young colleague at one's elbow in the clinic or ward is a medical student, they should be asked if they are agreeable to being examined by the student and told that a refusal will not offend. Patients should also be told that a student may be present in theatre and their permission to be examined by that student should be sought. It is simply not acceptable for a patient to find out, through a third party, that she has undergone multiple examinations of which she was unaware.

The labour ward continues to be a problem. Since the dawn of hospital obstetrics, the place has often been an educational cockpit with the streetwise medical student and student midwife competing for that obstetric prize—the normal multip in established labour. A successful resolution of this problem lies, as usual, in goodwill and good communication. The academic department should plan the entire labour ward component of the undergraduate course jointly with the chief midwife and agree the minimum number of students per shift which will fulfil, by the end of the course, the required number of labours observed and deliveries conducted. We may be thankful that the days have gone when packs of medical students roamed the labour ward, pouring in to observe or, more accurately, watch a distressed mother undergoing a manipulative or operative delivery.

A recurring complaint of medical students in the clinical years is that they are not given clear guidance at the beginning of the clinical course regarding what they are expected to know and be able to do at its end. Failure to give such guidance may mean that the department lacks insight into its value or, more ominously, that the department itself does not have a clear picture of its aims. Hence, it is reassuring to note that Biggs and colleagues find that most obstetric and gynaecology departments do provide such guidance, and in writing. Nor should attention to the strategic aims of the course be limited to the first day. On the metaphorical last day of the course, the students and the teachers should have the opportunity to express their perceptions of how the tactical management of the teaching matched the strategic aims of the course (Curzen 1987). At Aberdeen, among other centres, an annual educational autopsy is held at which staff, both academic and NHS, together with students, assess the educational viability of the course design and recommend changes. Such sessions should be noisy, entertaining and instructive. They should also be recorded and played back to the academic curricular group at leisure. An interesting variant of the exit poll occurs in Cape Town where the final OSCE (Objective Structured Clinical Examination) contains a station at which the students give the Head of Department, viva voce, their assessment of the course.

In conclusion, it is reasonable to award a beta-plus to our departments for their educative care of clinical students. The continuous watchful eye of the Association of Clinical Professors, the biennial national workshops on undergraduate education and the regular appearance of original and review articles on the teaching of our discipline, together bespeak a level of interest which is heartening. An alpha-rating, however, will have to await the inception of short courses in educational techniques for our registrars and lecturers, together with the final shedding of the old didactic pot-filling approach in favour of student-centred and self-directed learning as advocated by Elstein (1990). Above all, we must be crystal clear that if new material or methods are to be added to the course, their criteria for success, together with a time limit, should be laid down at the outset so that the innovation can be audited, and then either accepted or discarded. In other words, the same rigour should be applied to our teaching as is required for our clinical research and our patient care.

As obstetricians and gynaecologists, we have accepted that our central professional aim is the pursuit of excellence in the care of women. As teachers, that aim can be easily accommodated within the goals of undergraduate teaching as set out above. For, unless we see to it that our students receive a sufficient quality of education in the arts and crafts of our discipline, then we will fail to attract to its ranks the steady stream of graduate entrants which is essential for its progress and vitality.

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Reducing the risk of infection for obstetricians

The exposure of surgeons to needlestick injury and contamination with blood places them at risk of infection with hepatitis B virus (HBV) and more recently with human immunodeficiency virus (HIV). HBV has the lower mortality rate but is highly infectious and HIV, although much less infectious, carries a fatal prognosis. HBV would appear to be the most important occupational infection in health care workers in the developed world whilst HIV probably stimulates the most anxiety.

In addition to the greater infectivity of HBV, it is a much more resilient virus than HIV, surviving air drying and disinfection to a greater degree; this may facilitate transmission by environmental contamination of fomites.

Following needlestick injury from a patient with HBV, the seroconversion rate is 25% if the patient is HBe antigen positive and 5% if he is HB surface antigen positive in the absence of e antigen (Hadler 1990). Where the patient is HIV seropositive, needlestick injury carries a seroconversion rate of approximately 0·2% (Ippolito *et al.* 1990). Needlestick injury involving the injection of an inoculum understandably carries the greatest risk.

Rates of needlestick injury amongst surgeons are difficult to ascertain due to a low level of reporting, whereas glove puncture is readily measureable. Glove puncture represents potential needlestick injury and facilitates contamination of the surgeon's skin with infected material. The degree of contamination will depend on the size and length of time the perforation is present. Smith & Grant (1990) have shown that glove puncture in obstetricians occurs in 54% of caesarean sections and, where such perforations were recognized by the surgeon, 60% of them occurred during closure of the lower segment of the uterus. The frequency of glove puncture has been shown to increase with increasing length of the surgical procedure but, surprisingly, there is a lack of correlation with emergency surgery.

The seroconversion rate for HBV and HIV amongst health care workers is unknown following skin or mucous membrane contamination but is thought to be much lower than that following needlestick injury. There are only three recorded cases of HIV seroconversion following such exposure and each of these had unusual features, including delayed seroconversion and disseminated exposure in association with significant skin pathology.

In the USA it is currently estimated that 15 health care workers die annually from fulminant hepatitis, 1000 become HBV carriers and a further 200–300 will eventually die due to the chronic consequences of HBV infection, namely cirrhosis and primary hepatocellular carcinoma (Hadler 1990). Despite this, the current uptake of HBV vaccine amongst health service personnel in the UK is still inadequate (87% uptake in orthopaedic surgeons (Williams & Flowerdew 1990)). When HBV vaccine became generally available in 1982, uptake was initially poor, related perhaps to anxiety over its derivation. However, since 1987 genetically engineered vaccine has been available that is free from any potential pathogens and no adverse effects have been proven. More than 90% of infections with HBV in health care workers can be prevented by vaccination. In approximately 10%, an adequate course of vaccination will fail to mount a protective immune response, and presumably these individuals will remain at risk from infection (Westmoreland 1990). In view of its availability, reasonable cost, safety and effectiveness, we feel that HBV vaccination should be actively encouraged in all health care workers. Currently the medical profession are notoriously poor attenders at occupational health departments, but we believe this should become a requirement of their employment.

The standard HBV vaccination regimen comprises three injections with a 1-month interval between the first and second injection and a third injection 6 months after the first. This regimen results in peak antibody levels 1 month after the third dose, and therefore cannot provide rapid protection to individuals at high risk. It has been suggested that an accelerated vaccination schedule (0, 4 weeks and 8 weeks) with a booster vaccination at one year, if required, may result in more rapid protection. Antibody levels should be measured at approximately 3 months after the initial visit and if the result shows a non-protective response, a booster vaccination should be given. Thereafter antibody levels should probably be measured every 3–5 years and if they fall below a protective level, a further booster is required. If these measures fail to stimulate an adequate antibody response the person should be informed that he is not fully protected against HBV and should be advised to undergo post exposure prophylaxis with hyperimmune gammaglobulin as the need arises.

Reduction of risk for surgeons requires a one tier approach to infection control. Such a policy must include the wearing of gloves, waterproof gowns and goggles or protective spectacles during any procedure that may involve possible contamination with patients' body fluids. Additionally, any patient known to be seropositive should be placed last on the theatre list to facilitate thorough disinfection of the operating theatre following the procedure. A two tier infection control policy is likely to induce appropriate caution in the surgeon when he is aware of the patient's seropositivity, but also encourages a less careful approach in the management of those patients who are perceived to be at low risk of infection. Most patients have not been tested for either virus and of course many do not disclose 'at risk' behaviour. Furthermore, patients who have been recently infected may have negative antibody tests thus giving falsely reassuring results.

For an infection control policy to be effective, it must be universally implemented. A recent study conducted in an accident and emergency department demonstrated poor compliance with such a policy. Health personnel cited as reasons for lack of compliance, the perceived loss of manual dexterity and lack of time to implement the appropriate techniques. These excuses suggest complacency in the face of serious potential infection.

Double gloving reduces by a factor of six the frequency of inner glove puncture, with little loss in operator sensitivity (Matta *et al.* 1989). Glove manufacturers are currently developing gloves strengthened in the digits since this is the area most prone to puncture. Blunt tipped needles appear to reduce the frequency of glove puncture whilst being capable of perforating uterine muscle (J. M. Grant, personal communication) and cervical tissue (C. Hauxwell, personal communication). Special forceps for suturing the uterine wound during caesarean section are being developed and may reduce the risk of glove puncture. The use of staples during closure of the skin and internal wounds will further reduce the amount of suturing required, thus diminishing the puncture rate.

Nonoxynol-9 has been shown to have anti HIV properties *in vitro*. This has caused some surgeons, particularly in the USA, to smear nonoxynol-9 on their hands before donning surgical gloves. This is a practice with far from proven benefit. Nonoxynol-9 may increase skin permeability and thus, theoretically, increase the potential for infection with either HIV or HBV (Jeffries 1990).

Following exposure to potential infection by a needlestick injury a number of steps should be taken: the person should immediately decontaminate the wound by encouraging free flow of blood and by washing the area thoroughly with disinfectant Expert counselling should be available to discuss the risk of infection by HBV and HIV. Serum should be saved for possible future HIV testing. In the event of subsequent seroconversion this allows prior seronegativity to be confirmed.

In those not previously vaccinated for HBV, a course should be instituted as soon as possible and hyperimmune globulin administered within 72 h. The fast induction regimen for HBV vaccination is also appropriate for post-exposure prophylaxis. In view of the fact that HBV infection usually has an incubation period of 2 or more months, post-exposure vaccination alone may be sufficient in most cases.

Where a needlestick injury involves a known HIV seropositive patient, post exposure prophylaxis with zidovudine can be given, although this is of unproven benefit. To maximize the potential benefit, zidovudine should be given as soon as possible, preferably within 1 hour and not later than 24 hours after injury. It is currently prescribed at high dosage (1200 mg/day) for 6 weeks and as yet no serious side effects have been reported (Gerberding 1990). No data are available on the long term toxicity of this regimen. Due to the low HIV seroconversion rate following needlestick injury and the lack of enthusiasm shown by health care workers for placebo treatment, it is unlikely that the efficacy of zidovudine in post-exposure prophylaxis will ever be proved.

Reducing the risk of HBV infection in surgeons requires a substantially increased uptake of HBV vaccination. Current surgical practice also requires modification to reduce the risk of inoculation injury and skin and mucous membrane contamination. A high grade one tier infection control policy, coupled with the use of a combination of the measures described above, would greatly reduce the risk to obstetricians and gynaecologists of HBV and HIV infection.

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Undergraduate obstetrics and gynaecology in the United Kingdom and the Republic of Ireland, 1989

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Summary. Undergraduate obstetrics and gynaecology has given rise to concern at a time when the community has become increasingly sensitive about genital structure and function and human reproduction. A survey of clinical schools in the United Kingdom and the Republic of Ireland shows that an average of 11 weeks is available for undergraduate learning in the discipline. Nearly all schools provide written aims and objectives for clinical students. Pelvic examination is taught in what is concluded to be a sensible and responsible manner; students are expected to conduct an average minimum of eight deliveries. Family planning instruction is seen as generally inadequate. Comparison of clinical courses with those in Australia and New Zealand shows striking similarities. Undergraduate courses need to be under constant review and revision so that the best students are encouraged to see obstetrics and gynaecology as a desirable career path.

In 1988 the professors of obstetrics and gynaecology in the United Kingdom expressed their collective concern about the academic input to teaching in obstetrics and gynaecology (*British Medical Journal* 1989) They saw funding cuts and planning changes as likely to be seriously damaging to both medical education and research.

A medical fortnightly paper declared in May 1989: 'The MDU (Medical Defence Union) recently confirmed that obstetrics claims had increased so dramatically that young doctors were now refusing to enter the specialty' (Saunders 1989).

It was averred in 1988 that the undergraduate curriculum in obstetrics and gynaecology could be improved by teaching more about childbirth, antenatal care and fertility control and less about antenatal problems, the complications of labour and hormonal treatments of the menopause (Waterston 1988), while an editorial in the *Lancet* (1988) urged that course content be based on 'things that are especially needed' rather than on 'medical school power politics'. Another contributor to this debate declared that obstetrics and gynaecology provided an ideal and 'much more balanced' clinical training for undergraduates than that offered by medicine and surgery. Reproductive medicine was seen as 'the only hospital specialty broad enough to claim a place at the core of the undergraduate clinical curriculum' (Drife 1988) A survey of undergraduate obstetrics and gynaecology in USA and Canada saw a need for increased curriculum time (Beckmann *et al.* 1990).

Interest in undergraduate obstetrics and

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gynaecology is demonstrated in these comments, a welcome sign for the discipline at a time when all aspects of the curriculum are under critical review. Undergraduate programmes in the subject were reviewed as part of a comprehensive report on medical education (General Medical Council 1977). The present survey provides a new assessment of undergraduate programmes in a discipline in which theoretical and technical advances have been rapid, and about which social consciousness has been uniquely heightened.

Methods

A survey document of 22 questions was sent to the heads of all academic departments of obstetrics and gynaecology in the United Kingdom and the Republic of Ireland in December 1988, and replies were received from all 31 medical schools by November 1989. In four medical schools (Glasgow, Manchester, Nottingham, Leeds), replies were received from two clinical schools and the free comments from these schools have been included in analyses.

The questionnaire sought information on clinical schools, time devoted to the discipline, aims and objectives, learning opportunities and assessment methods. Schools were asked to list recommended textbooks and to indicate perceived deficiencies in current texts. Each school was asked to describe especially noteworthy features of its course and to list subjects which should be given highest priority in undergraduate learning in the 1990s.

An identical study was undertaken of the 14 clinical schools in Australia and New Zealand (Biggs & Humphrey 1990) and results of the two surveys are compared.

Results

Clinical schools

The 30 clinical schools in the UK reported a final year class size of 88–287 students in 1988–89 with an average of 144; the five clinical schools in the Republic of Ireland reported a class size of 66–120 with an average of 90 students.

Medical schools in the study provided an average block time for obstetrics and gynaecology of 11·5 weeks. The UK schools had times of 7–15 weeks, with an average time of 11·2 weeks. Ten of 26 schools provided 12 weeks. Block time was mostly in the second last year in 18 schools, mainly in final year in seven and mainly in the third last year in one. Three schools reported significant integration of clinical programmes; two described optional additional time in obstetrics and gynaecology—of 6 weeks in one case and 30 weeks in another. In one school, good students could elect not to take a 2-week revision course in final year.

Schools in the Republic had block times totalling between 8 and 26 weeks, four having between 8 and 12 weeks; the average time was 13 weeks. Four schools had block times of 6–8 weeks in the final year. Four schools in the UK reported recent or pending changes in time allocation, with increases of 1–2 weeks matching decreases of a similar order.

Instruction in basic human reproduction

Of 31 medical schools, 28 reported an introductory programme in reproduction. Three schools give this material at the start of the clinical course in obstetrics and gynaecology, while the remaining 25 described an introductory programme in the pre-clinical years, most commonly in the second year of the course (14 schools).

Two schools described an integrated preclinical programme which included human reproduction but most reported the courses as being offered by or under the direction of various combinations of departments or disciplines. The physiology department was involved in 19 schools, being the sole department mentioned in six of these; anatomy was cited as a contributor in 10 schools while obstetrics and gynaecology was identified as involved in 15 schools. Lectures, from 6 to 28 in number, were the main method of instruction described.

Introductory courses in basic clinical skills

Twenty-three of 31 medical schools described an introductory course in clinical skills in obstetrics and gynaecology, this usually occupying the first 1–2 weeks of the main clinical instruction block or the first part of each clinical attachment. Several schools reported an obstetrics and gynaecology component of a clinical skills introduction in the 'pre-clinical' year. Six schools replied that no skills course was given as a separate item.

Aims and objectives of the clinical course

In answer to the question 'are students given in writing the aims and objectives of the clinical course in obstetrics and gynaecology?', 23 of 35 clinical schools answered 'yes'. Papers given to students were provided by 21 schools, allowing an assessment of the stated aims and objectives. One school included in its introduction for students: 'Students welcome advice about what is expected of them ... (and) expect this advice and guidance to be well organized and clearly expressed.'

Nine clinical schools followed this dictum, providing operational objectives under a heading such as 'What the new graduate should be able to do in obstetrics and gynaecology' or 'What you are expected to learn'. Lists of 10–30 items followed, involving recognition, understanding, counselling of patients, manual skills and management of disorders.

Also noted in some responses was the teacher-centred approach in setting of objectives: '... provide students with instruction in reproductive medicine and the diseases of women ... (etc).'

The student instructions and handbooks of a number of schools indicating a commitment to written objectives, contained either very general statements of aims, or no aims or objectives at all. Several of the 11 schools which did not provide written objectives and the one which declined to answer this question wrote that the subject was covered in an introductory lecture.

Co-ordination of obstetrics and gynaecology and paediatric teaching

Of the 35 clinical schools 30 reported some degree of co-ordination, beyond that of being in adjacent blocks in a clinical rotation. Formal instruction in neonatal paediatrics took place during the obstetrics term in 20 schools. Several schools reported regular ward rounds or seminars involving both departments while one school reported an integrated obstetrics/gynaecology and paediatrics term (Purdie 1988).

Use of log books or cards by students

Student log books or cards were used by 20 of the 34 clinical schools which answered this question. Examples of logs were provided by most of the schools using them. At least 15 schools listed procedures that should be seen or done and at least nine required items to be initialled on completion. At least 13 schools used the completed card in an assessment of students' performance. Fifteen schools said they did not use logs.

Learning about speculum and pelvic examinations

All but one of the 35 clinical schools require supervised training in speculum examination; minimum numbers of procedures from 2 to 20 (average 7) were given by 19 schools but 12 specified that proficiency, as confirmed by a consultant, was the important measure. Experience in pelvic examination was gained principally in the outpatient department, under supervision, but several schools wrote of opportunities provided in the wards, especially labour ward and the post-natal ward. All schools but one supported examination of anaesthetized patients before operation, a number specifying that the patients examined were those previously clerked by the student concerned. The need for the patients' written consent was stressed in one response. Additional methods of instruction included introductory teaching sessions with slides and videotapes, and the use of plastic models in six schools. Two schools rejected the use of such models. Two schools were testing the use of 'gynaecology teaching assistants' for instruction in pelvic examination while one school vigorously opposed this approach.

Experience in vaginal delivery

Of the 35 clinical schools 30 gave minimum numbers of deliveries that students were expected to conduct. The range was from 4 to 15 with an average of 8. (Twelve schools expected five deliveries per student and ten expected 10).

Of five schools giving no number, two specified observed competence as the measure. The average number of deliveries conducted was in the range 5 to 23, with an average of 10 per student. Again, five schools gave no number but stressed proficiency as the yardstick.

Schools were asked whether difficulties were experienced in gaining deliveries for medical students. The five schools in the Republic of Ireland reported no difficulties. Of the 30 clinical schools in the UK, 12 described competition with midwives as a continuing though often inconstant problem, one school writing in dismay of the 40 deliveries conducted by each midwifery student when medical students had difficulty gaining five. Another school had moved towards a solution by allocating medical and midwifery students to different labour ward shifts. Other schools reported that medical students had better prospects of gaining experience at hospitals away from the main centre.

Practical tuition in family planning

The five schools in the Republic reported that instruction was limited to theory (three schools) or was not given (two schools) Of the 30 clinical schools in the UK, 19 required students to attend at least two family planning clinics in addition to lectures and seminars. In five schools only one clinical attendance was required, while in two schools, attendance was optional. One school reported that student attendance at clinics was poor, due to other commitments.

Recommended textbooks

Schools were asked to list the one or two textbooks most strongly recommended for undergraduate students. Since some schools were reluctant to advise students and others listed up to 10 books in total, any table of popularity must be viewed with caution.

Eight obstetric texts, six gynaecology texts and nine combined texts were named. Of these 23, only three had mentions in double figures (Beischer & Mackay 1986; Hull *et al.* 1986; Mackay *et al.* 1983).

Shortcomings of current textbooks

In answer to the question: 'Are there any topics which need to be added or strengthened in future editions or new textbooks?' there were negative responses like 'Recent editions frankly bad' and 'Textbooks largely out of date'. The author of one text responded '[no weaknesses] in mine' while another listed weaknesses and added 'I am doing this already'. There were 32 areas of specific comment which may be grouped as follows·

More needed on behavioural and organization matters

Communication skills (3 comments); ethical issues (5); psychological aspects, bereavement counselling; psychosexual counselling (2), medicolegal aspects, especially patient consent; social aspects; the politics of health care; hospice care and care of the dying; case loads in general practice; the need for antenatal visits and tests.

More on basic knowledge

Reproductive science, physiology and endocrinology (3), molecular biology; organic causes for gynaecological symptoms.

Techniques and skills

Less on mechanisms of labour; more on office obstetrics and gynaecology (3); cytology and colposcopy (2); ultrasound and imaging; prescribing in gynaecology; basic clinical skills; record keeping; statistics and epidemiology

More on clinical problems

Prenatal diagnosis (2); obstetrics and gynaecological presentations in other specialties; genetic counselling; puerperal problems; premenstrual tension, the menopause and hormone replacement therapy; male infertility; urinary incontinence; antepartum haemorrhage. Nine respondents, either specifically or by absence of comment, reported no weaknesses.

Hospital attachments and residence

Twenty-nine of 35 clinical schools arranged for attachment of students at a district general hospital (DGH) for a significant part of their obstetrics and gynaecology terms.

Eleven schools required residence of 2–10 weeks in the main teaching hospitals, either additional or as an alternative to the DGH experience. Students were expected to be resident during nights on call in 22 schools. Two schools said that no residence was expected while four others said that nights on call were optional. Several reported that students were spending less time in residence than formerly.

Notable features of clinical courses

Schools were asked about aspects of their courses to which they would like to draw attention and all but two replied. Four schools wrote of negative aspects—courses that were too short in three cases, and clinics that were badly organized in another. Positive comments were about students being actively involved as part of the clinical team (7 schools); integration of preclinical and clinical aspects and of different clinical disciplines (4); assessment methods, especially continuous assessment (2), pass/fail and honours exams, and use of the objective structured clinical exam (OSCE) (Harden & Gleeson 1979). Specific educational approaches were raised by 12 schools and included a basic skills course, student attachments to families, a weekly study day, a 30-week elective in obstetrics and gynaecology taken by up to 10 students per year, a fully-structured programme, and teleconferences (Hibbard *et al.* 1985). Two schools emphasized the importance of evaluation of the course by students and feedback to teachers, while one school wrote of 5 years spent in reorganization of the programme with a resulting surge of interest in obstetrics and gynaecology as a career.

Assessment of student proficiency

Thirty-three clinical schools provided details of assessment and examination procedures; 15 schools provided, under confidential cover, copies of recent exam papers. All schools used multiple methods of assessment, the most common being continuous assessment (32 schools), clinical exams (24), long essay questions (23), and oral exams (22). Written reports were used in assessment by 19 schools, most requiring case reports, while three required submission of relevant projects or essays and two called for reports on family attachments. Short essay questions were used by nine schools, modified essay questions by one and the OSCE by six.

Analysis of papers showed that most were of 3 h duration; most contained both long essays (between 1 and 4) and short essays ('Write one page on . . .' or 'Write 100 words on . . .'). Four also contained multiple choice questions, numbering between 10 and 60, all but one of which consisted of the Royal College of Obstetricians and Gynaecologists pattern of a stem and five yes/no items. The long essay questions were almost all on aetiology and management. The short essay questions also covered diagnosis and definition, whilst the multiple choice questions were mostly about definition, differential diagnosis, aetiology and prognosis.

Important topics for the undergraduate course

The survey enquired about topics that clinical schools considered most important for students in the 1990s. Five schools gave no listing, two because they had difficulty or disagreement in formulating an answer; three gave no answer at all. Thirty-two schools gave a range of answers but showed some widely held priorities. The topics most frequently listed were:

Antenatal care, normal pregnancy and labour, the puerperium	(17)
History taking and clinical examinations	(14)
Family planning	(14)
General gynaecology, including menstrual disfunction	(11)
Physiology and endocrinology of reproduction, including genetics	(10)
Communication skills and counselling	(9)
Abnormal obstetrics, including medical disorders	(9)
Gynaecological cancer, including screening	(9)

There followed, each with four or fewer listings, a range of topics in improved educational methods (emphasis on principles; problem solving; the English language); on educational content (ethics and legal aspects), counselling in psychosexual matters and social areas; obstetrical and gynaecological disorders (perinatal mortality and morbidity; infertility; emergencies in obstetrics and gynaecology; sexually transmitted diseases); and others (ageing and bereavement). Five schools made reference in the above topics to general practice aspects, while one sought improved working with midwives.

Feedback by students on courses of instruction

While schools were not asked about the assessment of their courses by students, seven schools made specific mention of such procedures or included forms for student comment in the papers they sent to us. Five schools provided students with forms for assessment of clinics, lectures, ward rounds, clinical instruction and even specific teachers, using a 1–5 or 1–6 grading ('excellent' to 'very poor', or 'very good' to 'poor'). Others invited students to comment in general or specifically on parts of the course.

Discussion

The General Medical Council (GMC) review of medical education in the British Isles in 1975/76 has an emphasis on teaching, which has changed in many education settings to learning. This is exemplified in the area of aims and objectives, which are becoming increasingly student-centred. We contend that students should be more and more self-motivated as they mature towards the end of the medical course and objectives listed as 'What the new graduate should be able to do' or 'What you are expected to learn' are a step in this direction.

The average duration of block teaching in the discipline in 1975/76 (General Medical Council, 1977) was 11·3 weeks with London schools having a little more time and Scottish and Irish schools a little less. Thirteen years later the average time is unchanged though average times in the Irish Republic are now longer and Scottish terms are still shorter. Two of those schools with the shortest block times saw this as a major and unsatisfactory aspect of their present programmes.

The 1975/76 GMC review found that most schools had detailed objectives but that only four provided (or planned to provide) a list of objectives to all staff. The importance of provision of operational objectives to students as well as staff is now widely recognized (Fisher & Levene 1989; Newble & Cannon 1987), and it is pleasing to see that most of the clinical schools in the present study gave written objectives to students or gave them verbally in an introductory lecture. It is suggested that objectives, setting out clearly what a student should be able to do by the end of each course, should be provided in every clinical discipline.

The GMC review looked at course review and revision and noted that most schools invited students' views. While the subject was not surveyed in the present enquiry the schools offering information showed a clear readiness to subject themselves to a detailed assessment by students, a process that is to be encouraged at a time when staff and programme review is becoming mandatory in higher education in Britain, as in Australia and New Zealand.

The GMC review devoted considerable attention to family planning and reported that 'practical knowledge about family planning services and techniques' was the objective of many courses. Students were only expected to be able to give elementary advice. At a time when family planning is an issue of increasing community interest and sensitivity, one might expect that undergraduate programmes would have become more active than in 1975/76. Results in the present survey showing required attendance at one or two clinics, even this being optional in some cases, suggest that emphasis on family planning is still inadequate in the undergraduate curriculum.

Instruction in pelvic examination has been a subject of special sensitivity in recent days. In New Zealand the ethical aspects have been addressed in a judicial enquiry (Cartwright 1988; Gillett 1990) and New Zealand clinical schools have instituted new procedures to meet public demands (Biggs & Humphrey 1990). Instruction in both speculum and bimanual examination remains a critically important part of the preparation of a medical practitioner. The ability to care for women, both in preventive and diagnostic directions, demands skill and understanding and clinical departments should not hesitate to affirm this stance. Faced with criticism by sections of the community, North American schools have turned to paid volunteers, often called 'Gynaecology Teaching Associates', to give instruction to students. The present study shows little enthusiasm and some aversion in the United Kingdom and Eire to this approach. Alternative methods include the use of slides and videotapes and perhaps recorded impressions of subjects about the examination; all should be employed to give a high level of confidence to students and to their teachers that skill and understanding have indeed been developed. On the basis of this survey we believe that a sensible and responsible approach is generally being used.

The textbooks recommended for students were nearly all written in the United Kingdom or Eire; the exceptions came from Australia from academics with British experience, or in two cases from North America. As in the recent report on Australian & New Zealand programmes (Biggs & Humphrey 1990), there is a call in this study for new or additional material on ethical issues and communication and counselling. Books in current use are shorter than in previous years, partly in response to student demands for inexpensive texts, but also because much detail has been trimmed. The trend is likely to continue.

The assessment procedures used in clinical schools cover a wide range; continuous assessment is used by 97%, clinical examination by 73%, the long essay question by 70% and oral examination by 67%. The papers provided by schools demonstrate the different potential of different written exercises. The long essay questions have few limits but almost all were used to test knowledge and attitudes on aetiology and management; short essay questions were mostly used to test definition and diagnosis; multiple choice questions tested definition, differential diagnosis; aetiology and prognosis, always on a yes-no basis that is, regrettably, less frequent in clinical care than writers of questions appear to believe.

The study gives clear guidance for the planner of a new clinical course. Advice from 32 clinical schools is that a course in the 1990s should give priority to about eight general areas. While the listing of reproductive physiology, normal pregnancy and labour, and general gynaecology will give no surprise, the inclusion of family planning gives confirmation of the comments made above, while the listing of communication and counselling skills is a recognition that society is better-informed on matters of reproduction and has higher expectations of medical practitioners than ever before.

A recent study of undergraduate programmes in Obstetrics and Gynaecology in Australia and New Zealand (Biggs & Humphrey 1990) shows patterns very similar to those evident in the present survey. Schools in the antipodes devote 11 weeks to the discipline in medical courses of similar clinical arrangement. The pattern of instruction in pelvic examination has similar uncertainties to those described in this study. Schools reported that each student undertook an average of nine vaginal deliveries and most schools in Australia and New Zealand reported difficulties arising from competition of medical and midwifery students. Textbooks named by schools included many of those listed in the present study; subjects suggested for inclusion in new books or editions included many in the area of patient contact, especially medical ethics, communication and medico-legal matters. Psychological aspects of the discipline were seen as needing more emphasis, as were basic subjects like genetics and immunology. The range is similar to that in the present survey. The priority topics for inclusion m an Australian and New Zealand curriculum were less clear than in the larger constituency of the United Kingdom and Eire, but the pattern was the same. It can be concluded that undergraduate education in obstetrics and gynaecology, in two parts of the world having a common background, has similar emphases and methods and similar expectations for the future.

The suspected reluctance of young doctors to pursue careers in obstetrics and gynaecology (Saunders 1989) has been confirmed in a recent Australian study (Biggs 1990). Obstetrics and gynaecology has long been one of the best appreciated parts of a medical student's course. The importance of carefully constructed and effective undergraduate programmes in stimulating an interest in the discipline needs to be widely recognized. A school in this study that spent 5 years in developing a new undergraduate programme reported a resurgence of interest in obstetrics and gynaecology as a career. The school is to be congratulated. More need to follow its example.

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Congenital and maternal cytomegalovirus infections in a London population

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Abstract

Objective—To determine if women at risk of having babies infected with cytomegalovirus (CMV) can be identified antenatally.
Design—Prospective serological and demographic study of pregnant women and virological study of their newborn infants.
Setting—Teaching hospital in London.
Subjects—3315 pregnant women and 2737 of their babies.
Main outcome measures—Quantitative detection of CMV IgG antibodies, qualitative detection of CMV IgM antibodies, demographic characteristics of mothers; qualitative and quantitative titration of CMV viruria in newborn.
Results—Congenital CMV infection was found in nine newborn babies (0·33%) two of whom had symptoms Serological testing of the nine mothers showed four primary and five recurrent infections; both of the symptomatic children were born in the latter group. Testing for CMV specific IgM antibodies or quantitation of IgG antibodies in early pregnancy sera could not differentiate those women at risk of giving birth to babies infected or damaged by CMV from the rest of the population. Quantitation of viruria confirmed that those babies most at risk of CMV disease have the highest titres of CMV.
Conclusions—(i) Since laboratory tests in pregnant women cannot reliably identify fetuses at risk of disease, screening for asymptomatic maternal infection coupled with termination of pregnancy cannot be recommended. (ii) Since 'immune' women can still give birth to babies affected by CMV, we propose that future CMV vaccines should be used to immunize children with the aim of eradicating CMV infection in preference to selective immunization of sero-susceptible females.

Cytomegalovirus (CMV) is the commonest infective agent causing intrauterine infection (Stagno *et al.* 1977). Serological studies in women giving birth to babies with this congenital infection have shown that women can transmit the virus following either primary or recurrent infection (Peckham 1983; Griffiths & Baboonian 1984; Stagno *et al.* 1986; Yow *et al.* 1988). Recurrent infection presumably results from reactivation of latent maternal virus during pregnancy rather than from reinfection because genetic analysis of virus strains from consecutive siblings born with congenital CMV infection has shown the viruses to be identical (Huang *et al.* 1980).

Since most babies born with infection do not appear to suffer, it is important to decide whether primary or recurrent maternal infection repre-

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sents the greatest pathological threat to the fetus. It is also important to investigate whether available laboratory assays can identify prospectively women at risk of having babies damaged by CMV. We have conducted a prospective study to identify babies with congenital infection and have followed them clinically to determine which developed adverse sequelae. By testing the antenatal sera from the whole cohort of women, which included mothers of congenitally infected children, it was possible to assess the usefulness of serological assays for CMV

Subjects and methods

Between March 1983 and December 1985 all babies born at this hospital were screened for congenital CMV infection by culture of urine collected in the first 3 days of life.

At the first antenatal visit pregnant women were asked to provide information about their country of birth and whether or not they were married. The husband's occupation was used to estimate 'social class', except when the woman was unmarried, when her own occupation was used for classification (OPCS 1970).

Culture of cytomegalovirus

Urine specimens were collected from the newborn infants and inoculated onto monolayer cell cultures of human embryo lung fibroblasts. The cultures were observed for the cytopathic effect typical of CMV for a minimum of 21 days.

If a baby was found to be excreting CMV a repeat urine specimen was obtained within 6 weeks of birth. Serial 10-fold dilutions of these urine samples were prepared and 3–4 replicates of each inoculated onto tubes of fibroblast cell cultures. The presence of cytopathic effect was recorded at 14 days post-inoculation and the urine titre of CMV was calculated in 50% tissue culture infectious doses/ml ($TCID_{50}$/ml).

Detection of specific antibodies

IgG antibodies specific for CMV were detected by radioimmunoassay as described previously. The quantity of antibody in each specimen was recorded as the binding ratio at a serum dilution of 1/400 (Griffiths & Kangro 1984). Antibodies of IgM class were also measured by radioimmunoassay after removal of rheumatoid factor by incubation with latex beads containing aggregated human IgG as described previously (Griffiths & Kangro 1984).

Definition of types of CMV infection

Primary infection was considered proven when seroconversion for CMV-IgG antibodies occurred or when CMV-IgM antibodies were found in the first available antenatal serum.

Proven recurrent infection was diagnosed when the mother of a congenitally infected baby was known to have had CMV IgG antibodies before conception.

Presumptive recurrent infection is a category used to define women who gave birth to congenitally infected babies but who had no detectable CMV-IgM antibodies in their earliest available antenatal sera. Since CMV-IgM antibodies have been shown to persist in pregnant women for up to 16 weeks following primary infection (Griffiths 1981; Griffiths *et al.* 1982), the absence of such antibodies makes a recent primary infection very unlikely but, since the assay is not 100% sensitive, a negative result cannot completely exclude primary infection.

Results

Prevalence of IgG antibodies

Antibodies of IgG class specific for CMV were found in 2000 (60%) of the 3315 women. The proportion of women who were seropositive was found to increase progressively with increasing age (see Fig. 1).

Congenital CMV infection

Congenital infection was identified in 9 of 2737 newborns tested (0·33%). One infant had jaundice, purpura and hepatosplenomegaly at birth consistent with cytomegalic disease at birth. This child and seven of the remaining eight children were followed as out-patients to the age of 3 years. The child with symptoms at birth had severe mental retardation and a further child who had been asymptomatic at birth developed progressive intellectual failure and, at the age of 3 years, he had severe motor incoordination and severe mental retardation. The remaining six children are developing satisfactorily, although one has behaviour problems and echolalia.

The type of maternal infection was related to the congenital infection. The results in Table 1 show that all of the infants infected *in utero* as a

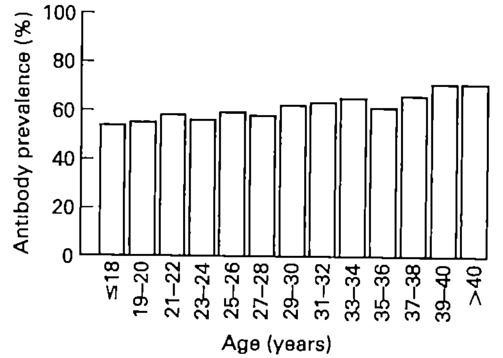

Fig. 1. Age-specific prevalence of IgG antibodies against cytomegalovirus

result of primary maternal infection remained well. The mother of the one child born with symptoms had proven recurrent CMV infection since she was shown to have IgG antibodies against this virus 10 months before becoming pregnant. Four women were seropositive at their first antenatal visits but no pregnancy sera were available. All gave negative results in assays for CMV-IgM antibodies and so are classified as 'presumptive recurrent' infections. One of the four children born following presumptive recurrent infection developed severe mental retardation. Thus, of nine children with congenital infection, four were associated with primary maternal infection and there were no adverse sequelae whereas two of the other five children associated with maternal recurrent infection were severely affected.

Urine samples were obtained for virus titration within 6 weeks of birth from eight of the infected children. The results in Fig. 2 show that the highest viral titre was found in the baby born with symptoms while the second highest titre was found in the baby who subsequently developed symptoms.

Table 1. Relation between type of maternal infection and congenital infection or disease

Type of maternal infection	Paediatric findings	
	Congenital infection	Symptomatic infection
Primary	4	0
Proven recurrent	1	1
Presumptive recurrent	4	1
Totals	9	2

Testing for IgM antibodies

CMV-IgM antibodies were assayed in 1632 (82%) of the 2000 CMV IgG positive sera. Ten of 1632 (0·61%) results were positive. One of these 10 women was delivered elsewhere and one had a missed miscarriage at 14 weeks. The remaining eight women gave birth to liveborn babies, although one had a small antepartum haemorrhage at 35 weeks. None of the eight infants had congenital CMV infection.

Quantification of IgG antibodies

To determine if relatively high CMV IgG antibody levels detected at the first antenatal attendance were predictive either of recent primary infections or of those destined to have congenitally infected babies as a result of recurrent infection, a cumulative frequency plot of antibody levels was constructed. Figure 3 shows that women in either group had CMV IgG levels which were evenly distributed throughout the range.

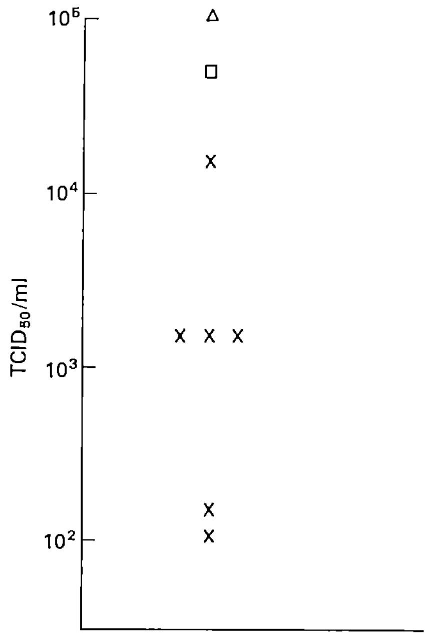

Fig. 2. Amount of cytomegalovirus (TCID$_{50}$/ml) found in neonatal urine and the subsequent development of symptoms in eight babies with congenital CMV infection. X = Asymptomatic, □ = Asymptomatic at birth but symptoms developed in the first year of life; Δ = Symptomatic at birth

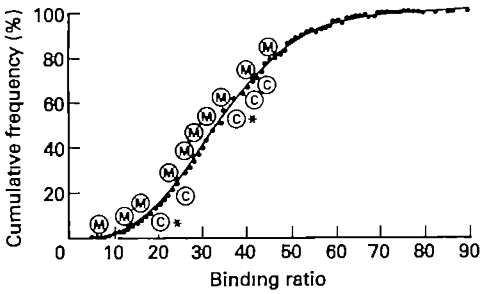

Fig. 3. Cumulative frequency plot of the amount of cytomegalovirus (CMV) IgG antibody found in pregnant women M = Samples also IgM positive; C = women who subsequently gave birth to a congenitally infected child, C* = women who subsequently gave birth to a congenitally infected child who was symptomatic.

Social characteristics of the population under investigation

Since our results were different from those reported elsewhere we investigated the demographic characteristics of our population to see if CMV infection was associated with the same types of individuals as found in other studies.

The prevalence of CMV IgG antibodies was found to vary significantly with a variety of demographic characteristics. The data presented in Table 2 show that women who were born in African, Asian or Arabian countries were significantly more likely to be seropositive than those born in European countries. Women in social class 1 were found to be significantly less likely to be seropositive than women in classes 3 manual and 6 or 7. In contrast, marital status had no influence upon the prevalence of antibodies to CMV.

Discussion

This study confirms other results from London which show that the overall rate of congenital CMV in this city is at the lower end of the worldwide ranges normally quoted (Peckham 1983) Only two children suffered as a result of their congenital infection and both were born to women who experienced recurrent infection during pregnancy (proven in one, presumptive in the other) compared to none of four whose mothers had primary infections. Only one previous case report (Ahlfors *et al.* 1981) had described congenital disease following recurrent maternal infection so we published the proven case from this series as an individual case report (Rutter *et al.* 1985).

If ours was the only study relating maternal infection to intrauterine transmission we might reasonably have concluded that recurrent maternal infection represents more of a threat to the fetus than does primary infection. In fact, published evidence suggests that the converse may be true with a statistically significant increase in the presence of symptoms at birth for babies born to mothers experiencing primary infection (Stagno *et al.* 1982). The demographic characteristics of our antenatal population showed the same factors associated with CMV infection as in other studies (Stagno *et al.* 1984; Griffiths *et al.* 1985; Yow *et al.* 1988). Clearly, it would be of great interest to define the relative contributions of primary and recurrent maternal infections to neonatal disease, but studies of such magnitude would be required that we doubt if the answer will ever be known. We believe, therefore, that planning for the future control of CMV disease should be based upon the recognition that both seropositive and seronegative women are at risk, so no reliance should be placed upon the ability of natural immunity to protect the fetus against CMV disease. Thus, while laboratory investigations continue into the development of non-replicating CMV preparations that could be considered as prototype vaccines, we feel that consideration should be given to how such preparations might be used.

If only primary maternal infection was important then immunization of seronegative girls before child-bearing age could be contemplated. However, since congenital infection and now congenital disease have been shown to result from recurrent maternal infection, females would have to be immunized as babies to prevent them acquiring infection in infancy or childhood. Due to increasing opportunities for acquiring CMV infection during adolescence, it would seem sensible to also consider the immunization of male infants so that they would not represent an infectious hazard to adolescent females. Thus, we believe that when a prototype CMV vaccine becomes available, it should be used for eradication of CMV infection rather than for suppression of primary infection in women of child-bearing age. This approach would be expensive but would have the added advantage of reducing the number of infectious individuals who could be blood donors or organ donors and so transmit this virus to immunosuppressed patients (Barbara & Tegtmeier 1987; Grundy *et al.* 1988).

Could disease caused by intrauterine CMV

Table 2. Demographic characteristics and cytomegalovirus (CMV) seropositivity

Demographic characteristic	No. women seropositive/ no. tested (%)		*P* value*
Country of birth			
Europe/N. America	1188/2367	(50%)	
Asian countries	390/436	(89%)	<0·001
African countries	314/352	(89%)	<0·001
Arabian countries	77/110	(70%)	<0·001
Totals	1969/3265	(60%)	
Social class			
1	170/312	(54%)	
2	614/1060	(58%)	
3NM	389/644	(60%)	
3M	325/522	(62%)	<0·05
4	131/217	(60%)	
5	20/50	(40%)	
6	129/185	(70%)	<0·001
7	94/129	(73%)	<0·001
Totals	1872/3119	(60%)	
Marital status			
Married	1650/2732	(60%)	
Single	318/530	(60%)	
Totals	1968/3262	(60%)	

*Compared to the first mentioned characteristic in each group

infection be controlled by selective termination of pregnancy? Since maternal CMV infections are almost always asymptomatic, laboratory screening of all pregnant women would be required to identify cases. We have reported previously on a low risk for individual fetuses born to mothers who seroconvert during pregnancy and so have been unable to recommend routine serological screening of antenatal patients for seroconversion (Griffiths & Baboonian 1984). Likewise, data from the present study show that the quantitation of IgG antibodies at the booking clinic would not provide any additional useful information. Furthermore, testing for IgM antibodies did not identify a group of women at especially high risk of having affected babies and so we can find no reason for recommending that pregnant women are tested by any serological method for evidence of CMV infection. A major problem with these studies has been that it has not been possible to test the fetus directly but only to test the pregnant women, knowing that only approximately one third of such women transmit the virus to the fetus (Griffiths & Baboonian 1984; Stagno *et al.* 1986; Yow *et al.* 1988). If it was possible to identify which women would transmit the virus it might improve the ability of antenatal serological testing to identify high risk pregnancies. One report suggests that the women who do transmit CMV are those who are unable to mount a prompt cell mediated immune response to primary CMV infection (Stern *et al.* 1986). If these results can be confirmed and extended, then the risk to an individual fetus might increase to a level where active case finding by means of serological surveillance for primary infection could be worthwhile. Such pregnancies might then be investigated by fetal blood sampling as has been described by Lange *et al.* (1982) for a severely affected 25 week fetus. However, the costs in terms of finance and expertise on the part of obstetricians and virologists, together with the possibility of raising anxiety amongst large numbers of women, must be taken into account if such a proposal is contemplated in the future. Furthermore, unlike rubella, CMV can cause damage at all gestational ages (Griffiths and Baboonian 1984, Preece *et al.* 1984; Yow *et al.* 1988) so that legal constraints may preclude the offer of selective termination even if the diagnosis of intrauterine infection has been made accurately.

An alternative way of potentially preventing paediatric disease due to intrauterine infection would be to identify at birth those infants with the worst prognosis and to give them antiviral drugs capable of suppressing CMV replication. The results presented here and in other studies show that infants with a poor prognosis can be detected soon after birth by the identification of those with high levels of viruria (Stagno *et al.* 1975; 1982). Although these infants have all acquired intrauterine infection much of the disease develops progressively during extrauterine life and so might be amenable to antiviral chemotherapy. At the moment, the only anti-CMV drugs available have serious toxicities or have to be given by the intravenous route, precluding the conduct of such studies at present. However, if drugs shown to be safer in adults are identified in the future, then the entry of children with a poor prognosis into placebo-controlled studies would be justified ethically and should be contemplated.

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Perinatal transmission of hepatitis B virus infection: a recommended strategy for prevention and control. A review

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It has been estimated that as many as 200 million persons—approximately 5% of the world's population—have chronic hepatitis B virus (HBV) infection (Sobeslavsky 1978). Although HBV infection is worldwide there is marked variation in its prevalence. In Western countries, the prevalence of hepatitis B surface antigen (HBsAg) carriers is only about 0·2% (Sobeslavsky 1980) compared to 10–20% in many parts of South-East Asia (Hsu *et al.* 1986), Africa (Botha *et al.* 1984; Marinier *et al.* 1985) and the Middle East (Sherif *et al.* 1985; Ramia *et al.* 1986). In contrast to the situation in Western countries where HBV infection is mainly a disease of adults (Szmuness *et al.* 1975; Gust 1982), most people in South-East Asia (Hsu *et al.* 1986), Africa (Botha *et al.* 1984; Marinier *et al.* 1985) and the Middle East (Sherif *et al.* 1985; Ramia *et al.* 1986) experience HBV infection in their early life. Infections in early life are particularly serious because they are more likely to result in the chronic HBsAg carrier state (Stevens *et al.* 1975; Beasley *et al.* 1982; Marinier *et al.* 1985). These carriers pose a problem because they may be infectious to others and also they may develop chronic liver disease including hepatitis, cirrhosis and hepatocellular carcinoma (Hadziyannis 1980; Beasley *et al.* 1981; Chung *et al.* 1983).

There are several mechanisms for the transmission of HBV and their relative importance also varies geographically (Francis *et al.* 1981; Beasley & Hwang 1984). Basically the transmission of HBV could be either horizontal (person-to-person) or perinatal (carrier mother to her infant). Perinatal transmission seems to play a major role in the spread of infection in the Orient (Okada *et al.* 1976; Beasley *et al.* 1977; Sy *et al.* 1986). However, in Africa (Prince *et al.* 1981; Greenfield *et al.* 1986; Coursaget *et al.* 1987) and the Middle East (Ramia *et al.* 1984; Al-Nakbil *et al.* 1986; Hyams *et al.* 1987), despite a relatively high prevalence of HBsAg carrier mothers, HBV infections usually do not occur perinatally but horizontal transmission in late infancy and early childhood seems to be the more important mode of spread. Irrespective of the mode of transmission, infection with HBV takes place in early life in most if not all parts of the world where HBV is endemic. Early interruption of mother–infant transmission of infection is probably the key to the control of HBV infection and its sequelae. This is a brief review of perinatal transmission of HBV and a recommended strategy for HBV control and prevention.

Factors predictive of perinatal transmission

During the past decade two markers of HBV infection, namely maternal HBeAg and HBV-DNA, have been shown to be reliable predictors of perinatal transmission of HBV infection. It is well established now that 85–90% of infants born to HBeAg-positive carrier mothers will develop HBV infection in the first few months of life and most of them will develop chronic infection and run the risk of developing cirrhosis and primary hepatocellular carcinoma later in life (Stevens *et al.* 1975). In contrast, infants born to anti-HBe-positive carrier mothers are much less likely to become infected (Stevens *et al.* 1975; Derso *et al.* 1978) and those who are infected do not become chronic carriers (Zanetti *et al.* 1982). The difference in the rate of perinatal transmission between HBeAg and anti-HBe-positive mothers may well be related to the level of circulating HBV par-

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ticles in the two types of carriers. The observation that the presence of HBeAg in the carrier mother was found to be a reliable indicator of perinatal transmission led to the suggestion that the discrepancy in the frequency of perinatal transmission among various populations is possibly due to the variation in the frequency of HBeAg among HBsAg carrier mothers Indeed, the rates of HBeAg in HBsAg carrier mothers vary considerably from one population to another (Beasley *et al.* 1977; Aldershville *et al.* 1980; Szmuness *et al.* 1981). The rate of HBeAg positivity varied from 30 to 40% among carrier mothers in the Far East (Okada *et al.* 1976; Beasley *et al.* 1977; Sy *et al.* 1986) compared with 16–20% among African carrier mothers and 7–12% among carrier mothers in the Middle East (Ramia *et al.* 1984; Al-Nakib 1986; Hyams *et al.* 1987). However, it must be mentioned that the differences in the duration of HBeAg-positivity may be due to ethnic or environmentally-related factors.

During the past 5 years, the circulating level of HBV-DNA, which is known to correspond well with the infectivity of HBsAg-positive serum (Bernigner *et al.* 1982), was found to be a more reliable indicator of perinatal transmission than HBeAg, DNA-polymerase or any of the other maternal HBV markers (Heijtink *et al.* 1984; Greenfield 1986; Lee *et al.* 1986; Ramia *et al* 1987). Recently, Ip *et al.* (1989) in a 3-year follow-up of 235 babies of HBeAg-positive carrier mothers suggested that the level of maternal HBV-DNA is the critical factor. The authors claim that when the mother's HBV-DNA level is <5 pg/ml the risk of development of HBV carrier state of her child is comparable with that of infants whose mothers are positive for HBsAg and anti-HBe. More interestingly, it was recently shown that the presence and level of HBV-DNA in HBsAG-positive carriers varies with racial origin being much higher in Orientals than in Africans (Karayanis *et al.* 1985). This finding might also explain the variation seen in the frequency of perinatal transmission of HBV among various populations.

Mechanisms of perinatal transmission

Mother-infant transmission of HBV may occur *in utero* (Ohto *et al.* 1987), perinatally (Stevens & Szmuness 1980; Chung *et al.* 1983) and postnatally (Beasley & Hwang 1983). Intrauterine transmission occurs only in 3–8% of infants born to HBeAg-positive carrier mothers, whereas most infections occur perinatally (Ohto *et al* 1987) or postnatally (Stevens & Szmuness 1980).

In a prospective study on the mechanism of mother-infant transmission of HBV in 37 mother-infant pairs from Hong Kong, Lee *et al.* (1978) detected HBsAg in 95% of gastric contents from newborns compared with 33%, 50% and 70% of amniotic fluid, cord blood and breast milk samples, respectively. This was the first time that HBsAg has been demonstrated directly in the gastrointestinal tract of babies born to HBsAg carrier mothers and thus provided direct evidence for the oral route of HBV infection during childbirth. The same authors (Wong *et al.* 1980) reported further that most of the infected babies contracted the infection as a result of swallowing infected fluid during delivery and materno-fetal transfusion during labour. Breast milk and saliva have also been suggested as possible mother-infant routes of transmission (Beasley *et al.* 1976). As to the possible mechanism of HBV infection *in utero*, it has been suggested that intrauterine transmission of HBV is closely related to placental leakage (Ohto *et al.* 1987). In Taiwan, Lee *et al.* (1986) showed that neonatal and maternal serum concentrations of HBV-DNA in HBeAg-positive carrier mothers at delivery were not parallel, indicating that intrauterine transmission of HBV was unlikely in most of these high-risk infants. The presence of HBV-DNA in the sera of some infants born to both HBeAg- and HBV-DNA-positive carrier mothers may have been due to HBV-DNA micro-leakage of maternal blood into the infant's blood circulation during tearing of the placenta at birth which may explain the failure of HB immunization in a number of high-risk infants.

Prevention of perinatal transmission: a recommended strategy for prevention and control

In a randomized blind controlled trial of the combined immunoprophylaxis approach using HB immune globulin (HBIg) plus vaccine, Beasley *et al.* (1983) showed that the combined efficacy was 94% compared with 71% and 75% with HBIg alone and vaccination alone, respectively. Studies conducted in the People's Republic of China (Xu *et al.* 1985), Taiwan (Lee *et al.* 1986), Hong Kong (Yeoh *et al.* 1986), Japan (Kanai *et al.* 1985), Korea (Chung *et al.* 1985) and the United States (Stevens *et al.* 1985) have demonstrated the efficacy of combined immunoprophylaxis in

Table 1. Routine paediatric vaccination schedule and hepatitis B virus (HBV) prophylaxis for infants of HB surface antigen (HBsAg)-positive mothers*

Age (months)	HB prevention schedule	HBV marker screening	Routine paediatric schedule
Birth	HBIg and HB vaccine		
1	HB vaccine		
2			Diphtheria-tetanus-pertussis (DPT)
4			DPT, polio
6	HB vaccine	HBsAg test†	
12–15		HBsAg and anti-HBs‡	
15			Measles, mumps, rubella
18			DPT, polio

* Adapted from the Centers for Disease Control (IPAC 1984; 1988).

† HBsAg-positive indicates therapeutic failure and a third HB vaccine dose need not be given

‡ Anti-HBs indicates therapeutic success.

preventing perinatal transmission of HBV infection. Recently, Delage *et al.* (1988) studied the efficacy of the combined passive-active immunization in 132 babies born to chronic carrier mothers of different ethnic origins (Haitians, Cambodians, French, Canadians, Vietnamese and others). Overall, 36 months after vaccination 92% of the responders were still protected (anti-HBsAg levels > 10 mIU/l). Equally important was their observation that maternal HBeAg status and the infant's sex or ethnic origin had no influence on antibody levels. The current recommendation of the Immunization Practices Advisory Committee (ACIP) (1988) for babies of HBs-Ag-positive mothers is the combined immunoprophylaxis approach: 0·5 ml of HBIg is administered intramuscularly within 12 h of birth, followed by HBV vaccine in three intramuscular doses (10 μg each). The first injection of vaccine should be given within 7 days of birth and may be given concurrently with HBIg but at a separate site. The second and third doses should be given 1 month and 6 months after the first dose. Because HB vaccine is an inactivated product and it is presumed not to interfere with other simultaneously administered childhood vaccines (Perillo *et al.* 1984), the ACIP (1984; 1988) recommends that the HB vaccine be given with other childhood vaccinations (Table 1).

Prenatal universal screening for HBsAg *vs.* universal vaccination of all newborns

In 1984 the ACIP recommended that pregnant women in HBV endemic areas and women in certain groups at high risk for HBV infection in non-endemic areas be screened for HBsAg during a prenatal visit and, if found to be HBsAg-positive, that their babies should receive HBIg and HB vaccine at birth. Since then, however, major problems have been encountered in implementing these recommendations (Delage *et al.* 1986; Kumar *et al.* 1987; Jonas *et al.* 1987; Summers *et al.* 1987; Wetzel *et al.* 1987). Outstanding among these, particularly in the non-endemic areas, has been the lack of knowledge among prenatal health care providers of the risk of perinatal transmission of HBV, the recommended screening and treatment procedures and the long list and diversity of the groups that are at high risk. The ACIP now believes that routine screening of all pregnant women, in non-endemic areas, is the only strategy that will provide acceptable control of perinatal transmission of HBV infections and the babies of HBsAg-positive mothers should receive the combined immunoprophylaxis treatment. The risk of later horizontal transmission of HBV by the mother or other infectious family members (Botha *et al.* 1984; Marinier *et al.* 1985) and the possibility of severe or even fatal hepatitis in infants born to anti-HBe-positive mothers (Shiraki *et al.* 1980; Sinatra *et al.* 1982) offer a rationale for providing immunoprophylaxis for all babies of HBsAg-carrier mothers, irrespective of the detection of other maternal HBV markers. Obviously, the universal screening of pregnant women for HBsAg means an additional cost. It has been estimated, at least in the United States, taking into account the cost of screening for HBsAg, plus the cost of HBIg, plus the cost of HBIg and the HB vaccine, that the cost of preventing one newborn infant from becoming a chronic

HBV carrier would be between $US 12 700 and $US 20 700 (ACIP 1988). Many investigators, however, argue that the costs and benefits of universal testing of mothers are comparable with those encountered in other widely implemented prenatal and blood-donor screening programmes (Arevalo & Washington 1988; Kane *et al.* 1988). Morover, the recent availability of recombinant HB vaccine, which is cheaper than the plasma derived vaccine, in addition to sensitive, specific and relatively cheap third generation screening tests for HBsAg, makes the programmes of universal screening of pregnant women for HBsAg, at least in some non-endemic countries, quite feasible. Programmes for universal screening of pregnant women are currently in progress in many parts of the world (ACIP 1988). In areas where HBsAg screening of mothers and providing HBIg for infants born to carrier mothers are not practical, the ACIP (1988) recommends universal vaccination of all newborn babies. This approach could prove to be successful in areas such as Africa and the Middle East where HBV is endemic but perinatal transmission occurs only rarely. In Western Europe, vaccine alone may also be adequate since perinatal transmission is also uncommon (Barbara *et al.* 1984; Boxall *et al.* 1986; Esteban *et al.* 1986). In the Far East, however, where HBV is endemic and perinatal transmission is a major route of transmission, inclusion of HBIg in the immunization schedule is necessary for the babies of HBeAg-positive carrier mothers (Ip *et al.* 1989). It should be stressed that the most effective strategy for controlling and preventing hepatitis B in countries where the disease is intermediate or highly endemic is to vaccinate all infants as part of the Expanded Programme on Immunization (EPI) of the World Health Organization (WHO) (EPI 1982). HB vaccine should be the seventh immunizing agent to be administered along with BCG, polio, DPT and measles vaccines. The recent increased availability and reduced cost of HB vaccine has made this strategy possible in many countries (ACIP 1988).

Finally, it must be mentioned that many parts of the world where HBV is prevalent, hepatitis D virus (HDV) is also endemic (Govindarjan *et al.* 1983; Ramia *et al.* 1988). Since infection with the defective HDV requires ongoing replication of HBV (Rizzetto 1983; Bonino & Smedile 1986), HBsAg carriers are always at risk of HDV infection with potentially grave consequences (Shattock *et al.* 1985; Bonino & Smedile 1986). Vaccination against HBV in early life would also provide protection against HDV later on (Bahakim *et al.* 1990).

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Early postoperative mortality following hysterectomy. A Danish population based study, 1977–1981

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Summary. The main objective of this cohort study was to analyse the early postoperative mortality after 'simple' hysterectomy for benign indications and to compare it with that of a randomly selected reference group of women matched for age. Registry data covering the entire Danish female population were used. Included in the study were all patients operated in the period 1977–1981. Patients were only included if no cancer was diagnosed and if no major co-surgery was performed (29 192 patients). Cancer patients were also excluded in the reference group (16 182 women). Mortality was studied according to characteristics of patients, their residential area, the surgical approach and operating hospital. Overall 47 patients died within 30 days of admission for hysterectomy (overall mortality 16·1 per 10 000). Only seven deaths were expected on the basis of the population sample, and adjusted for age, the relative risk (RR) for hysterectomy patients was 6·38 (95% CI 4·33–9·39). Early postoperative mortality increased with age, and the risk was elevated among emergency patients (RR = 3·22; 1·72–6·04). Patients with more than one diagnosis at discharge (RR = 4·53; 2·12–9.70) were at high risk, but early postoperative mortality was independent of surgical approach. Causes of death are discussed. Compared to the general population, patients who undergo 'simple' hysterectomy are faced with a sixfold risk of dying within 30 days, but a complete assessment of the risks and benefits of hysterectomy requires prospective studies of survival and morbidity, including quality of life for longer periods of time following operations.

In Denmark, as in other industrialized countries, hysterectomy is one of the more frequent operations (Dicker *et al.* 1982; Easterday *et al.* 1983; Wingo *et al.* 1985; Coulter *et al.* 1988). Every year, during the last decade, around 7000 women have had a hysterectomy annually in Denmark from a female population of about 2·5 million (the Danish Board of Health 1984 and 1986). Almost 80% of these operations were for benign indications.

Previous studies have shown substantial

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regional variation in population based rates of hysterectomy within Denmark (Andersen *et al.* 1987). The occurrence of regional variation suggests that highly individual criteria determine the use of hysterectomy for benign indications. Ideally, medical decision makers should have access to reliable information about the probabilities of all the relevant outcomes for the various treatments for a given condition and these outcomes should be available for subgroups of patients according to their age, health prior to treatment, perceived handicap associated with their symptoms, etc. (Weinstein *et al.* 1980). But, such full information is not currently available. Information on outcome of hysterectomy for different indications, as compared with alternative treatments, is virtually absent and, in particular, there is no evidence derived from randomized trials. Also, studies of hysterectomy have been based typically on experience from highly selected hospitals and the mortality is estimated from hospital records for the surgical admission with consequent variability in the period of follow-up (Grant *et al.* 1984; Amirikia & Evans 1979). Such studies have limited value and are not a reliable guide to the effectiveness and safety of the treatment under other circumstances. Population-based evidence on survival after hysterectomy is scarce, and any cost-effectiveness assessment of the procedure has been based on hypothetical rather than empirical life tables (Sandberg *et al.* 1985).

In the present study we have used registry data for the entire Danish female population to describe short term survival (30 days) after hysterectomy according to the surgical route and the patient's age at the time of operation. A random sample of the Danish female population—matched for age—provided a reference group. We estimated postoperative mortality in subgroups of patients according to various characteristics of the individuals themselves, the hospitals in which they were operated as well as the geographical area where they lived.

The main objective of this cohort study was to analyse the early postoperative mortality of 'simple' hysterectomy performed for benign indications and to compare it with that of a randomly selected reference group of women matched for age.

Subjects and methods

As of January 1978 there were 2·5 million women in Denmark, of whom 32% were 50 years of age and over. This population was served by 127 hospitals, of which 31 had special departments of gynaecology and obstetrics. Of 10 545 active physicians in Denmark, 6125 were employed in the hospitals and about 520 of these were in gynaecological departments.

Data sources

Data were collected from the following sources: the Danish National Hospital Register (inpatients), the Central Register for Hospitalized Psychiatric Patients, the National Population Register and the Cause of Death Register. Every person in the Danish population is identified by a unique registration number, and linkage of data over time as well as linkage across different data sources is highly accurate. The data bases cover the entire population of Denmark and—with minor exceptions related to international migration—complete follow-up is possible. For the current study, information about operations has been collected for the period from 1977 to 1981 and follow-up through the registries was possible until end of 1983.

The hospital register contains diagnostic information coded using the International Classification of Diseases (eighth revision, ICD-8, 1982), surgical information coded using the national classification of treatments (second revision 1980), in addition to administrative data and personal details about each patient. Information about admission to psychiatric hospitals before the hysterectomy was obtained from the psychiatric registry.

Patients and reference group

In the 5-year period, 1977–1981, 34 727 women resident in Denmark had a hysterectomy in Danish hospitals and were recorded in the Danish National Hospital Register. Inadequate information was available for 43 women leaving 34 684 women in the study.

In order to restrict our investigation to survival after 'simple' hysterectomy, cancer patients were excluded as were those who had other major surgery performed during the index admission (i.e., when the hysterectomy was performed). Major surgery at the same time as the hysterectomy (co-surgery) included operations on the thyroid gland, heart, breast, stomach, liver, gall bladder, intestine, colon, kidneys, urinary bladder or vagina. We excluded all patients who were registered with a cancer diagnosis in the Danish National Hospital Register in the last 6 month before or during the index admission. The application of these criteria led to the exclusion of 5492 patients of whom 98·6% had a diagnosis of cancer. This left 29 192 patients for survival analysis. The patients were categorized by the type of operation as follows: subtotal abdominal hysterectomy (3·5%), total abdominal hysterectomy (90·1%), vaginal hysterectomy (5·9%) and radical hysterectomy (0·5%).

The code for radical hysterectomy was used incorrectly by one particular hospital department which used this term for total abdominal hysterectomy and the removal of an ample vaginal cuff for carcinoma *in situ* of the cervix.

A random sample of Danish women, matched for age, was drawn from the population register to provide a reference group. All individuals who had been admitted to hospitals with a cancer diagnosis between 1977 and 1981 were excluded and mortality was estimated for 16 182 women who were alive at the mid-point of the period of observation.

Survival analysis

Postoperative mortality following hysterectomy was assessed by age and surgical approach for 29 192 patients. Unfortunately the discharge registry information does not include the exact date of operation but only the dates of admission and of discharge. Consequently 'postoperative mortality' has been estimated as '30 days mortality' from the date of admission, rather than from the date of operation. In addition, survival has been assessed for the period which began at the date of admission and ended 30 days after discharge. These two measures provide minimum and maximum estimates of the exact '30 days postoperative mortality'.

In the population sample, an analogy to '30 days mortality' was estimated, for a period covering the middle of the registration period (July 1, 1979).

The following potential determinants of postoperative mortality were investigated: age at time of operation, hospital admission during the year before the hysterectomy (those classified as gynaecological, psychiatric and other admissions); surgical approach for hysterectomy (subtotal abdominal, total abdominal, vaginal, radical); occurrence of minor co-surgery during the index admission; gynaecological diagnosis (pregnancy/delivery-related, precancerous and other diagnosis); number of diagnoses; type of admission (emergency *vs.* elective); geographical area (urban *vs.* rural); type of hospital (specialized *vs.* non-specialized).

Although the study includes a total of 29 192 hysterectomy patients, the amount of information available does not allow multivariate analyses to be performed, because very few deaths occurred within a month of the operation. As mentioned previously the population sample was matched for age before the exclusion of cancer patients—but not after, and consequently analyses of survival among various subgroups of patients compared with the population sample needed to be adjusted for age, using Mantel-Haenszel test and estimation with correction for continuity (Bereslow & Day 1987).

Results

Among 29 192 Danish hysterectomy patients with no major co-surgery, operated on for non-malignant diagnoses between 1977 and 1981, 47 women died within 30 days of admission (crude mortality 16·1 per 10 000).

Among the population sample of 16 182 Danish women without cancer diagnoses, 65 died within a period of 300 days. Number of deaths in a period of 300 days were used to enhance the stability of estimates of '30 days mortality'. Age specific mortality for the hysterectomy and the reference groups are presented in Table 1.

Although the general level of mortality seems to be low among hysterectomy patients, they are subject to a substantially higher risk of dying within 30 days of admission, when compared to the chosen reference population, adjusting for age (MH−RR = 6·38, $P<0{\cdot}001$).

A comparison of mortality in the three subgroups of hysterectomy patients categorized according to the surgical approach did not reveal statistically significant differences. The vast majority of patients (98%) had been discharged from hospital within 30 days of admission; 35% were discharged within 10 days, and 92% were discharged within 20 days of admission (total abdominal hysterectomies only).

Following patients for 30 days after discharge added another eight deaths so that 55 hysterectomy patients died during the period beginning with the date of admission and ending 30 days after discharge (crude mortality 18·8 per 10 000).

Table 1. Comparison of postoperative mortality (per 10 000 procedures) within 30 days of admission among 29 192 hysterectomy patients, by surgical approach, 1977–81. Reference group consisting of 16 182 Danish women, estimated age specific '30 days mortality'

	Surgical approach												Reference group		
	Subtotal abdominal			Total abdominal			Vaginal			All types*					
Age (years)	N	*n*	Mortality	N	*n*	Mortality	N	*n*	Mortality	N	*n*	Mortality	N	*n*	Mortality†
<40	278	0	0·0	9041	4	4·4	116	1	86·2	9525	5	5·2	5213	2	0·4
40–49	400	0	0·0	11 335	4	3·5	175	0	0·0	11 952	4	3·3	5740	9	1·6
50–59	189	0	0·0	4395	6	13·7	271	0	0·0	4868	6	12·3	2640	4	1·5
60–69	74	1	135·1	1104	6	54·3	562	0	0·0	1746	7	40·1	1448	8	5·5
70–79	49	1	204·1	388	8	206·2	496	7	141·1	934	16	171·3	880	19	21·6
>79	23	2	869·6	51	5	980·4	93	2	215·1	167	9	538·9	261	23	88·1
Total	1013	4	39·5	26 314	33	12·5	1713	10	58·4	29 192	47	16·1	16 182	65	4·0
RR§	8·86 (3·22–24·38)			7·22 (4·51–11·55)			‡			6·38 (4·33–9·39)			1		

Patients with diagnosed cancer and patients with major co-surgery excluded.

* Including 152 cases of incorrectly registered radical hysterectony (see text).

† Deaths in a period of 300 days were used to enhance stability of estimates of '30 days mortality'.

‡ Test of homogeneity of RR across age strata was rejected.

§ Age adjusted mortality risk ratio compared to reference group. The 95% confidence limits are shown in brackets

The Cause of Death Register includes up to three diagnoses per case and Table 2 shows the distribution of the direct cause of death within 30 days of admission for hysterectomy and for the reference group. In the hysterectomy group one of the associated recorded diagnoses were a cancer diagnosis in six, diabetes mellitus in five and obesity in two women. In the reference group the associated recorded diagnoses were a cancer diagnosis in two and diabetes mellitus in four women.

Mortality was compared among groups of patients according to the previously mentioned determinants (characteristics of the patients, their residential area, the operation itself and the operating hospital), controlling for age within the following categories: <50 years, 50–69 years, 70 and above (Table 3).

For two of the potential determinants (type of hospital and occurrence of co-surgery) it was not possible to obtain a single estimate of the relative risk of post-operative mortality as age modifies the effect of these determinants. Gynaecological departments accounted for 67% of all hysterectomies (26 deaths) while the remaining operations were carried out in other surgical departments (21 deaths). Compared with gynaecological departments the relative risk of early post-operative mortality in other surgical departments increased with age. For patients under 50 years the relative risk was 0·26 (0·03–2·09), between 50–69 years 1·27 (0·42–3·89) and above 70 years 2·98 (1·34–6·62). Minor co-surgery occurred with 52% of all total abdominal hysterectomies and the relative risk of early postoperative mortality compared to hysterectomy alone also increased with age; being for patients under 50 years 0·18 (0·02–1·43) and above 3·08 (0·73–13·05).

Patients admitted to hospital as emergencies experienced a higher level of mortality than those who were elective admissions (MH–RR = 3·22, P<0·001) (all ages).

Patients, who were discharged after hysterectomy with more than one diagnosis, experienced a substantially increased risk of dying within 30 days of admission as compared to those discharged with only one diagnosis (MH–RR = 4·53, P<0·001).

None of the other potential determinants was associated with statistically significant differences.

Discussion

Very large populations are required for the study

Table 2. Cause of death for all hysterectomy patients who died within 30 days of admission and for the reference group

Cause of death	No. of deaths			
	Hysterectomy group		Reference group	
Cardiovascular disease		28		38
Arteriosclerotic heart disease or other heart disease	9		11	
Acute myocardial infarction	9		12	
Embolism/Thrombophlebitis	7		1	
Apoplexy	3		14	
Pulmonary disease		6		9
Pneumonia, acute bronchitis	5		9	
Other respiratory disease	1			
Gastrointestinal or hepatic disease		4		3
Cirrhosis of the liver	2		2	
Appendicitis	1			
Ileus	1			
Cholelithiasis			1	
Renal diseases				3
Complication to the operation itself		5		
Bleeding	4			
Lesion of ureter	1			
Pregnancy/delivery-related		2		
Embolism	1			
Toxaemic antepartum bleeding	1			
Other causes		2		12
Infection in uterus, vagina or external genitalia	1			
Suicide/accident together with a psychiatric diagnosis			4	
Accident			1	
Dehydration			1	
Lupus erythematosus, systemic			1	
Cancer (mamma, rectum)			2	
Diagnosis missing	1		3	
Total deaths		47		65
Number of women	29 192		16 182	

of rare events such as early postoperative mortality following hysterectomy. Even as many as 29 192 operations do not allow powerful conclusions. The organization of a sufficiently large randomized trial is hardly practicable, and clinicians and patients are currently forced to rely on observational studies, such as this one, as a basis for decision making. Our results reflect the experience of a total national population, and avoid the potential biases associated with results derived from selected university hospitals.

The main objective of this study was to investigate survival after 'simple' hysterectomy and patients were excluded if a cancer had been diagnosed or major co-surgery was performed during the index admission. We excluded all patients for whom a cancer diagnosis had been recorded by the hospital registry in the 6 months before, as

Table 3. Estimated effects of potential determinants of early post-operative mortality controlled for age only (Mantel Haenszel)

Determinants		*n*	N (%)	RR (95% CI)
Admission 1 year before hysterectomy:				
*Gynaecological	No	21	12 274 (52·5)	1·00
	Yes	19	11 090 (47·5)	1·79 (0·94–3·41)
Psychiatric	No	46	28 862 (98·9)	†
	Yes	1	330 (1·1)	†
*Other	No	32	20 806 (87·7)	1·00
	Yes	8	2558 (12·3)	2·11 (0 97–4·57)
Type of gynaecological diagnosis*				
Obstetric	No	45	28 975 (99·3)	†
	Yes	2	217 (0·7)	†
Precancerous	No	44	25 901 (88 7)	†
	Yes	3	3291 (11·3)	†
More than one diagnosis at discharge	No	8	13 840 (48·4)	1·00
	Yes	39	15 352 (52·6)	4·53 (2·12–9·70)
Type of admission:				
Emergency	No	33	26 434 (91·6)	1·00
	Yes	14	2758 (9·4)	3·22 (1·72–6·04)
Type of hospital:				
Specialized	No	21	9487 (32·5)	‡
	Yes	26	19 705 (67·5)	‡
Geographical area				
Capital		9	7467 (25·6)	1·00
County of capital		6	5965 (20·4)	0·98 (0·35–2·75)
Small cities		16	7140 (24·4)	1·91 (0·84–4·33)
Rural		16	8620 (29·6)	1·65 (0·73–3·74)
Occurrence of co-surgery (total abd)	No	9	12 504 (47·5)	‡
	Yes	24	13 810 (52·5)	‡

* Includes 23 364 operations after January 1, 1978.
† Too small numbers of deaths.
‡ Heterogeneity of RR across age strata (see text).

well as during, the index admission. Despite these exclusions we found that the death registry included cancer diagnoses in six of the recorded deaths. Likewise, there were two cancer deaths in the reference group, according to the death registry. It is well known that there are various sources of inaccuracy in registration, such as incomplete information, coding errors and simple data entry errors. In this instance, however, it is likely that the hospital diagnoses were recorded at discharge (and entered into hospital registry) before the autopsy results were available, whereas the latter were subsequently recorded by the death registry. Other studies have compared data from the Cause of Death Register, the National Hospital Register and the Danish Cancer Register and have shown that 6% of cancer patients registered by the Cancer Register were not registered in the National Hospital Register, while the opposite was found in 5% (Storm 1984; Østerlind & Jensen 1985). Nevertheless this inconsistency between the registries does not influence the overall results in our study.

The definition of postoperative mortality varies from study to study (Amirikia & Evans 1979; Dicker *et al.* 1982; Roos 1984; Wingo *et al.*

1985; New York State Department of Health 1988), thus making comparison of the results of different studies difficult. Wingo *et al.* (1985) estimated the postoperative mortality at the time of hospital discharge (317 389 total abdominal hysterectomies and 119 972 vaginal hysterectomies). He found that the maximum estimates of the crude mortality rate of women who had a hysterectomy was 12 per 10 000, but the estimates were substantially higher for pregnancy—as well as cancer—related hysterectomies (53·4 and 102·6 per 10 000 respectively). Hysterectomies for other reasons were followed by a crude mortality rate as low as 5·1 per 10 000. A report from New York State Department of Health (1988) included 93 152 hysterectomy patients from 1984 to 1986. The crude mortality rate at the time of discharge (35 per 10 000) remained stable throughout the 3 years and the rate was highest for cancer-related cases (202 per 10 000), lower for pregnancy-related cases (72 per 10 000) and lowest for other causes (11 per 10 000). Among those for whom hysterectomy was the principal procedure, the crude mortality rate at the time of hospital discharge was 25 per 10 000 and was highest for cancer-related cases (157 per 10 000), lower for cases other than cancer and pregnancy (8 per 10 000) and lowest for pregnancy-related cases (0 per 10 000). No reference groups were included in these two studies.

We studied mortality within 30 days of admission, but we had no information about the date of operation. Our estimated postoperative mortalty (16·1 per 10 000) may thus slightly underestimate the true mortality up to 30 days after operation. However, an estimate based on the entire period from the date of admission until 30 days after discharge provides an exaggerated upper limit (18·8 per 10 000).

For most of the Danish hysterectomies a total abdominal approach was used (90·1%), and no more than 5·9% of the operations were vaginal hysterectomies. This practice pattern is in contrast to the United States where the vaginal approach is more prevalent (about 25%) (Easterday *et al.* 1983; Wingo *et al.* 1985). In our study the postoperative mortality was independent of the surgical approach, while both Wingo *et al.* (1985) and the New York State Department of Health (1988) found that the mortality was lower for the vaginal than for total abdominal approach. These contradictory results might be explained by the small number of Danish hysterectomies performed by other surgical approaches than the total abdominal (type two error). Different patient selection account for some of the discrepancy, but a prospective randomized study would have to be conducted to answer this question.

We found that early postoperative mortality increased with age for all three surgical approaches. However, in agreement with other previous studies (Wingo *et al.* (1985) we found that young women were subject to elevated mortality irrespective of surgical route. This might be explained by the serious reasons necessitating hysterectomy in young fertile women, such as hysterectomy related to pregnancy and delivery.

The attempt to identify subgroups of high risk patients by means of registry data was not very successful, but given the small number of deaths, this lack of discrimination might well be explained as a type two error. Not surprisingly, we found that emergency admissions were associated with a substantially increased mortality. While information about emergency admissions might provide a prognostic indicator of increased risk the number of diagnoses at discharge— a powerful predictor of mortality—is of little help for pre-surgical decision making. Multiple diagnoses at the time of discharge might be a result of chronic disease, but may also reflect the occurrence of complications in connection with the operation itself.

Early post-operative mortality (within 30 days of admission) appears to be low (16·1 per 10 000) and, compared to other surgical operations, it seems warranted to classify hysterectomy as a 'safe intervention'. However, it should be noted that these results originate from patients who did not have diagnosed cancer and who had no major co-surgery. Previous analyses have asumed that patients selected for elective hysterectomy had a better prognosis than women in the general population (Sandberg *et al.* 1985). Contrary to this assumption we found that Danish patients who undergo a 'simple hysterectomy' actuallly face a risk of dying within 30 days which is about sixfold that of women in the general population. Whether the prognosis for these patients before hysterectomy might have been better without the operation cannot be determined on the basis of observational evidence.

An increased risk of cardiovascular disease following hysterectomy has been observed in several studies (Centerwall 1981). However, it is debatable whether women with an increased risk of cardiovascular disease may have an increased propensity to undergo hysterectomy, or to what extent premenopausal hysterectomy contributes to the occurrence of cardiovascular disease.

In our study, which includes both pre- and postmenopausal hysterectomy, cardiovascular disease accounted for 29 deaths (including the woman with embolism related to delivery), while no more than four were expected on the basis of the age matched population sample (RR = 7·18, 95% CI 4·37–11·78, $P<0·001$). This result confirms the previously reported excess in cardiovascular deaths following hysterectomy. However, early postoperative mortality due to other causes was similarly increased with 19 deaths observed among hysterectomy patients and only 3–4 expected (RR = 5·40 (95% CI 2·91–10·03, $P<0·001$). Cardiovascular disease accounted for 60% of all deaths among hysterectomy patients but even in the reference group 58% of all deaths were due to this particular cause.

In our population-based study the vast majority of operations were performed with a view to improving the quality of life rather than to prolonging life. Seen in this context it is necessary to take into consideration the risk of early postoperative death when choosing between surgical and other methods of treatment. A complete assessment of the risks and benefits of hysterectomy for benign indications requires longer follow-up studies of survival and morbidity. Also, it is important to assess functional status and quality of life before and after hysterectomy. Further prospective studies are needed.

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Angiotensin II levels in hypertensive and normotensive pregnancies

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Summary. We measured circulating angiotension II by radioimmunoassay in women with pregnancy-induced hypertension ($n = 54$), and compared these values with those obtained in women with normal pregnancy ($n = 18$) and in non pregnant women ($n = 20$). Pregnant women had statistically significantly higher plasma angiotensin II [mean (SD): 41·3 (12·6) pg/ml] than non-pregnant women [29·2 (11·3) pg/ml; $P<0{\cdot}004$]. Angiotensin II concentrations in women with pregnancy-induced hypertension [mean (SD): 31·7 (16·2) pg/ml] were, on average, 25% lower than in normal pregnancy ($P<0{\cdot}003$) and resembled those obtained in non-pregnant women. The lowest angiotensin II levels were found in women with more severe forms of pregnancy-induced hypertension, such as proteinuric or superimposed pregnancy-induced hypertension. Review of the published studies on angiotensin II and our data suggest that the conflict among studies on angiotensin II levels in pregnancy-induced hypertension is largely due to the heterogeneity of the study populations in the various reports.

The renin-angiotensin system is activated in pregnancy resulting in high levels of renin substrate, renin enzyme, plasma renin activity and angiotensin II in the maternal circulation (Derkx *et al.* 1986; Symonds 1988; Broughton Pipkin 1988) Angiotensin II, the active component of the system, is one of the most powerful naturally occurring vasopressors and plays a role in the control of salt and water homeostasis (Broughton Pipkin 1988). These characteristics link it closely to arterial blood pressure control and to the phenomenon of pregnancy-induced hypertension.

It is clearly established that the pressure response to angiotensin II is enhanced in pregnancy-induced hypertension compared with normal pregnancy (Symonds 1988; Broughton Pipkin 1988). There is also agreement that, in comparison with normal pregnancy, plasma renin activity is lower in women with pregnancy-induced hypertension (Chesley 1978; Carr & Gant 1983; Broughton Pipkin 1988). No such agreement exists for concentrations of the angiotensin II octapeptide (ANG 1-8) in the maternal circulation. Whereas some authors reported no differences in angiotensin concentrations between normal and hypertensive pregnancies

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Table 1. Clinical characteristics of the women in the various study groups

Study group	No of women	No. of nulliparae	Age (years)	Gestational age (weeks)	Maximum blood pressure (mm Hg) Systolic	Diastolic
PIH	41	27	27·1 (4·0)	33·3 (3·5)	159 (16)	103 (8)
Non proteinuric	17	9	27·7 (4·0)	35·0 (2·6)	151 (12)	100 (6)
Mild proteinuric	6	6	27·4 (5·7)	35·2 (3·0)	149 (9)	97 (6)
Severe proteinuric	18	12	26·0 (3·2)	31·2 (3·3)	170 (16)	107 (8)
Superimposed PIH	13*	13	32·5 (5·4)	31·4 (3·5)	174 (22)	113 (14)
All hypertensive women	54	40	28 2 (4·9)	32·9 (3·5)	163 (19)	105 (11)
Normal pregnancy	18	8	28·2 (3·5)	34·0 (2·1)	130 (10)	75 (7)
Non pregnant women	20	—	28·7 (5·5)	—	—	—

* 8 had proteinura The results are mean (SD) values
PIH = pregnancy-induced hypertension.

(Massani *et al.* 1967; Gordon *et al.* 1973; Pedersen *et al.* 1985), others found angiotensin II levels to be either higher (Symonds *et al.* 1975; Symonds and Broughton Pipkin 1978) or lower (Weir *et al.* 1973; Weir 1975) in pregnancy-induced hypertension than in normal pregnancy. Still others found that angiotensin II levels were reduced only in 'pre-eclamptic', but not in 'uncomplicated' hypertensive pregnancies (Beilin *et al.* 1983).

In view of these conflicting data, we have reviewed published studies, measured angiotensin II levels in women with pregnancy-induced hypertension, with and without pre-existent hypertension, and compared the results with those obtained in normal pregnancies and in non-pregnant subjects.

Patients and methods

The study groups consisted of 54 women admitted to hospital with pregnancy-induced hypertension, 18 normal pregnant volunteers recruited at random from the antenatal clinic, and 20 non-pregnant volunteers with regular menstrual cycles recruited from hospital staff and medical students. Clinical characteristics of the hypertensive and control subjects are summarized in Table 1.

Hypertension was considered to be present if there were two consecutive diastolic blood pressure measurements (Korotkow's phase IV) of ≥90 mm Hg ≥4 h apart. Pregnancy-induced hypertension without pre-existent hypertension was subdivided into proteinuric and non-proteinuric depending on whether there was proteinura of ≥0·3 g/24 h. Those with proteinuric pregnancy-induced hypertension were further classified as severe if the condition was associated with any of the following: one diastolic blood pressure reading above 120 mm Hg or two readings above 110 mm Hg, proteinura of ≥3·0 g/24 h, haemolysis, elevated liver enzymes, platelet count below $<10 \times 10^7$/l or evidence of neurological irritability. Pregnancy-induced hypertension, which occurred in women with pre-existent hypertension, was classified as superimposed pregnancy-induced hypertension.

All women had an unrestricted salt intake; sodium excretion measured in a random sample of 20 hypertensive women ranged between 25 and 150 mmol/24 h. All women rested for 30 min in the left lateral position before 20 ml blood was collected from an antecubital vein in the right arm into tubes containing 8-OH-quinoline-5-sulphonic acid (17·5 mM final dilution) on ice. Plasma was separated immediately by cold centrifugation at 9000 g, quickly frozen in liquid nitrogen and stored at −80°C. In samples collected on 8-OH-quinoline-5-sulphonic acid neither production nor degradation of angioten-

Table 2. Angiotensin levels in pregnancy-induced hypertension compared with pregnant and non-pregnant controls

Study group	No. of women	Angiotensin II (pg/ml) Mean (SD)
1. Pregnancy-induced hypertension	54	31·7 (16·2)
2. Normal pregnancy	18	41·3 (12·6)
3. Non pregnant women	20	29·2 (11·3)

Wilcoxon rank sum test: 1 *vs* 2: $P<0·003$; 2 *vs*. 3: $P<0·004$; 1 *vs*. 3 not significant

Table 3. Mean (SD) angiotensin II levels in subgroups of women with pregnancy-induced hypertension (PIH)

	Angiotensin II (pg/ml)			
	All patients		Patients without antihypertensive treatment	
	n	Mean (SD)	*n*	Mean (SD)
PIH				
Non proteinuric	17	40·1 (22·6)	12	47·3 (23·2)
Mild proteinuric	6	26·6 (2·5)	5	26·5 (2·8)
Severe proteinuric	18	27·5 (12·9)	6	28·0 (16·4)
Uric acid <0·35 mmol/l	9	38·8 (26·0)	5	53·5 (26·8)
Uric acid ≥0·35 mmol/l	32	30·8 (14·8)	18	33·4 (17·4)
Before 37 weeks gestation	34	33·1 (18·6)	17	39·7 (22·9)
After 37 weeks gestation	7	30·2 (13·8)	6	32·2 (14·0)
Nulliparae	27	31·6 (16·8)	15	34·8 (20·0)
Multiparae	14	35·1 (19·6)	8	43·8 (21·3)
Superimposed PIH	13	26·3 (10·6)	2	37 1 (3·0)

sin II occurred. Levels were not influenced by the addition of enalaprilic acid, a known inhibitor of angiotensin converting enzyme. In plasma samples spiked with 50 000 cpm ^{3}H-ANG 1-8 (specific activity 34 Ci/mmol; Amersham Int, Amersham, England), all of the radioactivity was recovered in the ANG 1-8 octapeptide fraction on high-pressure liquid chromatography and none in the fractions corresponding to the smaller angiotensin peptides (Hanssens *et al.* 1990).

Angiotensin II concentrations were measured directly in plasma by radioimmunoassay based on the technique described and assessed by Lijnen *et al.* (1978). The ANG 1-8 MRC-standard A 70/302 was diluted serially to contain from 200 pg to 1·25 pg/0·5 ml assay buffer (0·13 M sodium borate buffer, pH 8·0, with 0·25% (w/v) bovine serum albumin). Aliquots of 0·3 ml plasma were diluted with 0·2 ml assay buffer to which 5000 cpm ^{125}I-labelled ANG 1-8 (1250 Ci/mmol; New England Nuclear, Boston, Mass., USA) in 0·1 ml diluted rabbit serum were then added, followed by 0·1 ml angiotensin antiserum (final dilution 1/560 000). After 48 h incubation at 4°C, bound and free peptides were separated with 0·7 ml cold suspension of dextran-coated charcoal; the bound fractions were counted. Cross-reactivities of the antiserum raised against 5-Ile ANG 1-8 amide with various angiotensin peptides were: ANG 1-8: 100%; ANG 2-8: 165%; ANG 3-8: 500%; ANG 4-8: 130% and ANG 1-10. 2%; cross-reactions with the tetrapeptides ANG 5-8 and ANG 1-4 were <0·001%. Assay blanks were below 1 pg and the limit of detection was 2·5 pg. Intra-and inter-assay coefficients of variation were 6·6 and 18% respectively.

The Wilcoxon rank sum test and Spearman's correlation were used for statistical analysis.

Results

Pregnant women had statistically significantly higher plasma angiotensin II levels than non-pregnant women (Wilcoxon, $P<0·004$, Table 2). The total group of hypertensive women had angiotensin levels which were on average about 25% lower than in normal pregnancy (Wilcoxon, $P<0·003$), and comparable with levels in non-pregnant women (Table 2).

Subanalyses of the data in relation to type and severity of hypertension, parity and gestational age are shown in Table 3. The lowest angiotensin II concentrations were found in women with proteinuric and with superimposed pregnancy-induced hypertension, irrespective of whether they had received anti-hypertensive treatment or not (Table 3). Women with non-proteinuric pregnancy-induced hypertension and especially those without antihypertensive treatment had levels which deviated far less from the levels

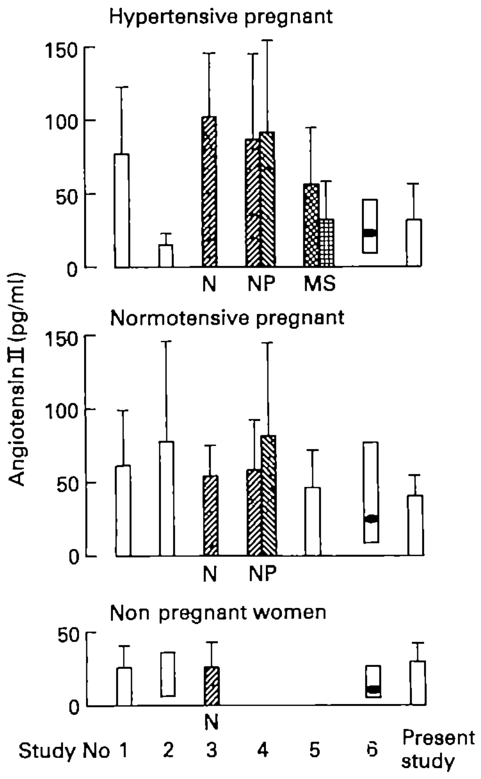

Fig. 1. Summary of all published data on angiotensin II levels measured by radioimmunoassay in women with pregnancy-induced hypertension The bars represent mean (SD) except for study 6 which refers to median and range. The study numbers refer to: (1) Gordon *et al.* 1973; (2) Weir *et al* 1973, Weir 1975; (3) Symonds *et al.* 1975 (all nulliparae), (4) Symonds & Broughton Pipkin 1978 (N: nulliparae, P: parae); (5) Beilin *et al.* 1983 (M: 'uncomplicated hypertension', S: 'Pre-eclampsia'); and (6) Pedersen *et al* 1985.

observed in normal pregnancy. Women with uric acid levels ≥0·35 mmol/l, especially those without antihypertensive treatment, had lower angiotensin levels than women with uric acid levels <0·35 mmol/l. There were only minor differences, which were not statistically significant, between samples in term and preterm gestations (<37 weeks) or between nulliparous and parous women (Table 3)

Within subgroups of normotensive and hypertensive women there was no direct relation between systolic or diastolic blood pressures at the time of sampling and angiotensin II levels (Spearman's correlation). Neither was there a significant relation between angiotensin II levels and maximum systolic or diastolic blood pressures measured at any time before samples were obtained.

Discussion

In the last 25 years, seven published studies have addressed the question of whether circulating angiotensin II concentrations differ between hypertensive and normotensive pregnancies. The earliest of these studies (Massani *et al.* 1967) was based on a bioassay, which probably measured not only angiotensin II, but also angiotensin I; there was no difference between 'toxaemic' and normotensive pregnancies and this study is not considered further. The other six studies, of which one was reported in two publications (Weir *et al.* 1973; Weir 1975), were based on radioimmunoassay of angiotensin II after extraction from plasma using different extraction techniques and different antibodies. Although the levels in non-pregnant and normotensive pregnant women were roughly comparable in these studies, there were wide differences between the mean levels in women with pregnancy-induced hypertension as shown in Fig. 1.

These differences may, in part, relate to differences in assay techniques but they cannot be explained entirely in this manner. For instance, the reports with the highest (Symonds *et al.* 1975; Symonds & Broughton Pipkin 1978) and the lowest (Weir *et al.* 1973; Weir 1975) levels were based on the same extraction procedure. It is unlikely that the differences between studies relate to different policies of salt restriction, since 5 of the 6 reports (detailed in Table 4) mentioned that women had an unrestricted diet, while the 6th (Beilin *et al* 1983) provided no information on this aspect. None of the reports mentioned whether samples were taken in the left lateral position, but in five studies the women had been recumbent for at least 30 min before samples were obtained and only one report (Gordon *et al.* 1973) dealt with ambulatory patients. Some of the difference could be due to varying contributions of different ANG peptides to the immunoreactive angiotensin II measured, especially since several authors provide no information on the cross-reactivity of their antiserum. None of the data, which we reviewed, have used high pressure liquid chromatography to separate ANG 1-8 specifically.

The most likely explanation for the differences in angiotensin II levels among these studies is that they may have included women with different forms or severity of hypertensive disease. Indeed, when criteria such as gestational age, mean blood pressure, and the occur-

Table 4. Clinical characteristics of hypertensive women included in the various studies of angiotensin II levels in pregnancy-induced hypertension

Authors	No of women*	Gestational age (weeks)	Maximum blood pressure (mmHg)		No with	
			Systolic	Diastolic	Proteinuria	Treatment
1. Gordon *et al.* (1973)	6 (4)	[37-40]	Not given	Not given	2	?
2 Weir *et al.* (1973) & Weir (1975)	8 (7)	± 34	± 163	± 107	8	0
3. Symonds *et al.* (1975)	16 (16)	39·6 (1 2)	133 (12)	13 (11)	8	0
4 Symonds & Broughton	22 (22)	± 39	138 (11)	97 (9)	11	0
Pipkin (1978)	14 (0)	± 40	135 (7)	93 (6)	4	0
5 Beilin *et al* (1983)	12†	36·0 (2.4)	126 (8)	74 (7)	0	2
	8‡	33.7 (3.9)	142 (20)	85 (11)	?	3
6. Pedersen *et al.* (1985)	14 (8)	[32-39]	[148-205]	[95-120]	14	0
7 Present study	54 (40)	32 (3.5)	163 (19)	105 (11)	32	29

* No. of nulliparae is shown in parenthesis.
† Mild hypertension.
‡ Pre-eclampsia
Results are mean (SD) or [range] values.

rence of proteinuria are considered as indicators of this variation (Table 4), the two studies with the lowest mean angiotensin II levels (Weir *et al.* 1973; Pedersen *et al.* 1985) apparently contained more women with early onset proteinuric hypertension. This explanation appears to be substantiated also by the difference between 'uncomplicated hypertension' and 'pre-eclampsia' in another study (Beilin *et al.* 1983; Fig. 1).

Nevertheless, from all the studies published since 1970 it remains unclear whether angiotensin II levels are lower in pregnancy-induced hypertension than in normal pregnancy of similar duration. Unfortunately, all of the studies are so small (Table 4) that important differences may have been overlooked. Unequivocally lower levels in pregnancy-induced hypertension than in normal pregnancy were reported only by Weir *et al.* (1973), who studied a mere eight hypertensive women and eight matched controls and used a paired statistical test to demonstrate the difference. Only one further report mentioned that women with pre-eclampsia had significantly lower angiotensin II levels than women with normal pregnancy, but women with so-called uncomplicated pregnancy-induced hypertension had higher levels than women with normal pregnancy (Beilin *et al.* 1983; Fig. 1).

Our study was conducted on a much larger group of patients with a severity of disease that was comparable with that in the studies of Weir *et al.* (1973) and Pedersen *et al.* (1985) in terms of early gestation at which the disorder manifested itself, mean blood pressure and the occurrence of proteinuria (Table 4). The mean angiotensin II level in our hypertensive women is comparable with the level obtained in these two studies and with the levels in women with pre-eclampsia studied by Beilin *et al.* (1983) Our study shows that angiotensin II levels are statistically significantly suppressed in pregnancy-induced hypertension to about 75% of the levels observed in normal pregnancy of similar duration. Further analysis of the various subgroups was consistent with this conclusion.

It is known that a clinical diagnosis of pregnancy-induced hypertension is more likely to be substantiated by the typical features on renal biopsy in nulliparae than in multiparae (Fisher *et al.* 1981). Although all women in our study had early antenatal care and blood pressure measurements, which should reduce the likelihood of an erroneous diagnosis of pregnancy-induced hypertension, we found that angiotensin II levels tended to deviate more from levels in normal pregnancy in our hypertensive nulliparae than in our hypertensive multiparae

Similarly, angiotensin II levels in women with pregnancy-induced hypertension deviated more from the mean in normotensive women if there was proteinuria than if there was no proteinuria. When grouping women according to uric acid levels, another indicator for the likelihood of correct diagnosis and severity of disease (Lancet & Fisher 1956; Thurnau *et al.* 1983), women with high uric acid levels had reduced angiotensin levels. Levels also tended to deviate more from levels in normal pregnancy if pregnancy-induced hypertension was superimposed on pre-existent hypertension than if it was not. All of these features reinforce our conclusion that the decrease in angiotensin II levels in pregnancy-induced hypertension is a reality rather than an artefact.

The lower angiotensin II levels in pregnancy-induced hypertension could result from a reduction in angiotensin II production, an increase in metabolism or a higher uptake by angiotensin receptors. Recent electronmicroscopic observations (Hill *et al.* 1988) on the sparsity of renin granules and poorly developed granular endoplasmatic reticulum in the juxtaglomerular apparatus in women with pre-eclampsia suggest that reduced renal renin production is the most likely explanation for the lower angiotensin II levels in pregnancy-induced hypertension.

In conclusion, our study appears to provide an answer to the contradictions in the literature in that angiotensin II levels are indeed reduced in pregnancy-induced hypertension and that the size of this reduction relates to the severity of disease.

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Anti-Kell in pregnancy

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Summary. A review of data on haemolytic disease of the newborn (HDN) collected in Newcastle upon Tyne over 25 years revealed 194 pregnancies in which anti-Kell was the only antibody detected. Sixteen affected babies were born. None was hydropic, three had very severe disease but all survived. There were also three stillbirths, none of which had post-mortem appearances of HDN. The highest recorded anti-Kell titres in individual patients ranged from 1/1 to 1/2048 and bore no relation to the severity of the disease. Of the eight pregnancies in which amniotic fluid examination predicted a high risk of stillbirth, half resulted in unaffected babies. We suggest that haemolytic disease caused by anti-Kell is less severe than suggested by some workers. The use of guidelines developed from the study of Rhesus disease to determine the need for intervention in women with anti-Kell may be inappropriate.

The decreasing frequency of Rhesus haemolytic disease of the newborn (HDN) has resulted in an increase in the proportion of other red cell antibodies in the aetiology of HDN. Anti-Kell is now the single most important non-Rhesus cause of HDN. Over 90% of the population is Kell negative and the number of affected pregnancies is small. In the United Kingdom most women with anti-Kell antibodies have produced them in response to previous blood transfusion with Kell positive blood. A number of case reports and two studies (Caine & Mueller-Heubach 1986; Farr & Gray 1988) have described a poor outlook for babies affected by anti-Kell.

Data on pregnancies affected by HDN have been collected for over 25 years in Newcastle upon Tyne. Our impression that the outcome in Kell sensitized pregnancies might be better than that described in the literature led us to review the data from the last 25 years with respect to pregnancy outcome and the value of antibody titres and amniotic fluid examination as predictors of outcome.

Subjects and methods

All pregnancies managed in Newcastle between 1965 and 1989 in which anti-Kell was detected were reviewed. Women with additional antibodies were excluded. Antibody titres were measured by the indirect antiglobulin (Coombs) test at the Regional Transfusion Centre and the highest documented titre for each woman was recorded. In general, amniocentesis was carried out when criteria established for investigation of Rhesus HDN were fulfilled (Walker 1971), but the decision to investigate was affected by a variety of factors in individual women Spec-

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Table 1. Distribution of affected and unaffected infants in 185 pregnancies with anti-Kell

	Anti-Kell titre											
Severity of disease	1/1	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	1/2048
Unaffected	19	7	23	14	23	20	18	19	11	8	3	4
Mild	0	3	1	1	1	2	1	0	1	0	0	0
Moderate	0	0	0	1	0	1	0	0	0	1	0	0
Very severe	0	1	0	0	0	0	0	1	0	0	1	0
Total	19	11	24	16	24	23	19	20	12	9	4	4
% affected	0	36	4	13	4	13	5	5	8	11	25	0

No 'severe' cases or stillbirths See Subjects and methods for definition of grades of severity.

trophotometric analysis of amniotic fluid was performed as described previously (Knox *et al.* 1965) and the results were expressed as the ratio of percentage transmission 520 nm: percentage transmission 490 nm. The baby was considered to be affected if a positive direct Coombs test on cord blood was recorded. The severity of HDN was graded on clinical, haematological and serological findings using the criteria developed in Newcastle for HDN caused by anti-D (Walker 1971). Briefly these were:

Mild: Coombs +ve. No treatment.

Moderate: Coombs +ve. Cord Hb>11g/dl and requiring transfusion.

Severe: Coombs +ve. Cord Hb<11g/dl or bilirubin >5mg/dl (>85μmol/l).

Very severe: Coombs +ve. Cord Hb<7.5g/dl or hydropic with HB>7.5g/dl.

Stillborn: (including miscarriage before 28 weeks).

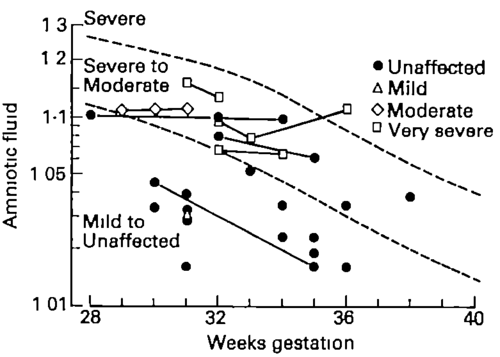

Fig. 1. Amniotic fluid ratios for affected (open symbols) and unaffected (closed symbol) babies. Linked points indicate repeated amniotic fluid examinations in the same pregnancy. The three zones on the chart predict likely severity of haemolytic disease (HDN) due to anti-D

Results

Over the 25 year period, anti-Kell was the sole antibody detected in 194 pregnancies in 180 women. There were three stillbirths and 191 livebirths. None of the stillbirths had features consistent with HDN at post-mortem examination. There were 16 babies with a positive direct Coombs test born to 12 mothers. Of the 16 babies 10 had mild, three moderate and three very severe HDN. None was hydropic and all survived.

Antibody titres were available in all 16 pregnancies with affected babies and in all but nine of those unaffected. The values ranged from 1/1 to 1/2048. Titres associated with unaffected and affected babies together with severity of HDN are shown in Table 1. There was no correlation between antibody titres and whether or not the baby was affected nor between titre and severity of disease.

Amniotic fluid was investigated in 21 pregnancies, only five of which resulted in affected babies. In seven pregnancies at least one repeat test was performed. The ratios are plotted against gestation (Fig. 1) on a chart which was developed to predict pregnancies affected by anti-D most likely to result in stillbirths and therefore justifying intervention (Fairweather *et al.* 1976). In four pregnancies which resulted in unaffected babies, amniotic fluid ratios fell in the range associated with moderate to severe disease.

Discussion

The chief finding of this study is that it confirms our impression that HDN due to anti-Kell is not as severe in Newcastle upon Tyne as some published studies might suggest. Individual case reports will almost inevitably reflect obste-

Table 2. Outcome of Kell haemolytic disease of the newborn (HDN)

Study	Affected babies	Fetal losses	Neonatal deaths	Survivors
Pepperell *et al.* (1977)	6	1	2	3
Caine & Mueller-Heubach (1986)	13	3	1	9*
Farr & Gray (1988)	9	8	1	0
Total	28	12	4	12
Present series	16	0	0	16

*Including one with hydrops

tricians' worst experiences and reports of single pregnancies affected by anti-Kell which result in very mild disease are unlikely to be published. We therefore examined in more detail three studies which contained data on several patients. The outcome of these reported pregnancies, together with the results from the present study are shown in Table 2. We have not identified a single stillbirth due to Kell sensitization in the past 25 years. The cause of death in the three fetal losses in the present series is not known, but they did not appear to be caused by HDN. For comparison Caine & Mueller-Heubach (1986) recorded 10 terminations and 5 spontaneous fetal losses in 114 pregnancies associated with anti-Kell which resulted in unaffected babies. Although we looked at more affected babies than others, our study is still small enough that a significant stillbirth rate could easily be missed. This criticism may be equally applied to the other three studies which may have observed by chance an exaggerated incidence of fetal loss caused by anti-Kell. Under-reporting of lack of stillbirths in pregnancies associated with anti-Kell may have contributed to an unbalanced picture in the literature. The suspicion remains that the complication which provides the major indication for amniocentesis, ie, stillbirth, is rare in this disease.

After the detection of anti-Kell in a pregnant woman, the next step is to determine which pregnancies are likely to do badly. It is important to determine the genotype of the father of the fetus because 90% are Kell negative and further investigation is unnecessary. The present study has shown that the range of titres associated with unaffected babies is so great that even if the father is Kell positive it is not possible to predict an affected fetus. The mothers of half the unaffected babies had titres of >1/16, while half of those with affected babies, including one very severely affected, had titres of ≤1/16. This lack of correlation makes it difficult to select those pregnancies which should have amniotic fluid investigated, and no amniocentesis was performed in 11 pregnancies where the baby was affected. In some instances, the patient was referred too late, whilst in others, the obstetrician did not consider that amniocentesis was justified. There is little help from the published series, none of which includes data on antibody titres in pregnancies which resulted in unaffected babies.

This problem is further compounded by difficulties in interpretation of spectrophotometric analysis of amniotic fluid. The accuracy of prediction of stillbirth, and thus the need to intervene in the pregnancy, is well established in HDN due to anti-D. The method of analysis used in Newcastle upon Tyne is at least as good as others, and after 34 weeks gestation better than others, at predicting stillbirth due to anti-D (Savage *et al.* 1966). Experience of Rhesus HDN in Newcastle upon Tyne encompasses many thousands of affected babies (Walker 1971) and hundreds of stillbirths in contrast to the small numbers reported worldwide to be affected by anti-Kell. In the present study amniotic fluid ratios proved unsatisfactory. Although we identified no stillbirths as being due to anti-Kell in this series, eight pregnancies subjected to amniocentesis had amniotic fluid ratios which, in Rhesus HDN, would be regarded as indicating risk of stillbirth. In fact, half resulted in unaffected babies. Although amniotic fluid ratios overall proved effective in distinguishing affected from unaffected babies (specificity 76%; sensitivity 80%) this is of little clinical importance. Inaccuracy of prediction is not restricted to overdiagnosis of affected fetuses. Caine & Mueller-Heubach (1986) in their series, Berkowitz *et al.* (1982) and Birkenfeld *et al.*

(1980) have described cases in which falsely reassuring results of amniotic fluid analysis were associated with severe fetal anaemia, hydrops or intrauterine death.

The two studies (Caine & Mueller-Heubach 1986; Farr & Gray 1988) which provide data on amniotic fluid analysis, express reservations about its value in the management of Kell HDN. Both suggest that such pregnancies should not be managed in the same way as those affected by anti-D. Our data support this view. There is no proof that this disease behaves in the same way as Rhesus HDN. Although we believe that use of methods developed from experience with anti-D to predict risk of stillbirth due to anti-Kell is inappropriate, our study does not contain enough data to resolve this issue. Experience of Kell HDN will never approach that of Rhesus HDN and it is unlikely that the accuracy of prediction using these techniques will improve. Whether confirmation of Kell group and diagnosis of fetal anaemia by cordocentesis will have a major impact on pregnancies associated with anti-Kell remains unknown. The best prospect of reducing morbidity due to anti-Kell is to prevent transfusion-induced sensitization of women to the Kell antigen. To achieve this all women before and during childbearing age should receive Kell compatible blood whenever they are transfused. This policy which has already been adopted elsewhere (Pepperell *et al.* 1977) obviously has implications for the National Blood Transfusion Service as well as individual blood banks. The problem of how best to deal with the rare cases of true isoimmune disease will remain, but the number of women needlessly subjected to invasive and potentially hazardous investigations and the risk of giving birth preterm to unaffected babies will be reduced.

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Life events and low birthweight—analysis by infants preterm and small for gestational age

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Summary. Social stress was assessed in 92 women with low-birthweight babies and 92 controls using the detailed LEDS measure of life events and severe chronic difficulties. The low-birthweight group was divided into preterm delivery ($n = 40$), small for gestational age (SGA) ($n = 40$) and mixed groups. Multivariate analysis was performed using a binomial-logit model to examine whether social factors were independently and significantly associated with low birthweight once the effect of demographic factors, obstetric factors and smoking/drinking were taken into account. Comparison of preterm births with controls indicated that three factors were significantly associated: a previous low-birthweight baby, severe life event/difficulty and bleeding during pregnancy. For SGA babies the factors were: previous low-birthweight baby, low social support and smoking. By using a reliable measure of life events and adequate numbers of low-birthweight babies, this study overcame the potential inaccuracies of previous studies and indicates a more specific relation between social stress and low birthweight.

Low birthweight remains the single most important factor in infant mortality and morbidity in the Western world (Dunn 1984), and reduction in its rate has been named by the WHO as one of the global indicators of progress towards the projected goal of health for all by the year 2000 (World Health Organisation 1984). Yet the evidence linking social factors with low birthweight has been described repeatedly as methodologically inadequate (Oakley, 1985, Istvan 1986, Levin & Defank 1988, Stein *et al.* 1987) and has been challenged recently as an artefact attributable to factors such as cigarette smoking, maternal age, height, and parity (Morrison *et al.* 1989; Brooke *et al.* 1989). Attempts to increase birthweight by provision of additional social support appear to have failed unless they have included reduction of smoking as a specific aim (Oakley 1985; Spencer *et al.* 1989). It therefore appears that the role of stressful life events may be eclipsed by the more dominant biological variables and smoking, although it has been argued that this is an area of research where psychological and social variables must be studied concurrently with biological ones (Oakley 1989).

Only three studies have used a reliable measure of life events. Other studies have not used a detailed interviewer-based method (Creed 1985) so previous studies may have shown positive results because of reporting bias (Nuckolls *et al.* 1972; Newton *et al.* 1979, Berkowitz & Stanslav 1983; Reeb *et al.* 1987; Omer *et al.* 1986). Of the three studies, Newton devel-

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oped his own scale (Newton *et al.* 1979) which was used prospectively to avoid retrospective bias (Newton & Hunt 1984); the other two (Stein *et al.* 1987; Brooke *et al.* 1989) used the interview for recent life events (described by Paykel 1984). No previous study has used the LEDS method described by Brown & Harris (1978). This method is superior to others because greater attempts are made to prompt recall, life events are more clearly defined before the study and the rating of severity of events is made by independent raters who are blind to both the experimental group and the mental state of the subjects at the time of interview. These aspects of method all counteract the natural bias for 'ill' subjects to record more life events than healthy comparison subjects. It was this bias which led to the spurious result of Stott (1958) in which mothers who had given birth to infants with Down's syndrome recalled more 'emotional shocks' during pregnancy than others who had had healthy babies.

The major limitation of the first two life event studies was the number of low-birthweight babies included. The sample described by Newton & Hunt (1984) included only 18 babies under 2500 g, which is possible why they did not find an association of low birthweight with known obstetrics factors, such as previous obstetric complications. They did find an association between objective major life events and both preterm delivery and low birthweight, though the effect did not add significantly to that attributable to smoking.

Stein *et al.* (1987) only studied 14 low-birthweight babies, and did not find an association with smoking, adverse life events or chronic difficulties, though low income was significantly associated. When birthweight was used as a continuous variable, smoking and low income were significantly related to birthweight but not to preterm birth.

Brooke *et al.* (1989) used a similar method to that described by Stein *et al.* (1987) and concluded that life events have no effect on birthweight but the method of analysis must be considered inadequate Brooke *et al.* (1989) used total number of life events in their analysis whereas Newton & Hunt (1984) had demonstrated previously that 'objective major events', but *not* total number of events were related to low birthweight. Brooke *et al.* (1989) did comment that analysis of particular events may be more informative.

The present study was designed to include an adequate number of low-birthweight babies, to measure life events by the reliable and precise method described by Brown & Harris (1978) and to examine whether the relation between life stress and birthweight was consistent for infants born preterm and small for gestational age (SGA). It was performed in an inner city health district that has one of the highest rates of low birthweight (10%) in the country (Central Manchester Health Authority 1988). The design was a case-control study to ensure that adequate numbers of mothers with low-birthweight babies were studied.

The project was granted approval by the Central Manchester Health Authority Ethics Committee.

Subjects and method

A consecutive series of women, resident within the Central Manchester Health district, who gave birth to a baby weighing <2500 g at St Mary's hospital between 1st March and 31st July 1988 formed the experimental group. Women whose pregnancy was terminated because of medical intervention and those who had multiple births or abnormal babies were excluded. Following each index delivery, the next woman to give birth to a baby >2500 g was interviewed as a control subject. Similar exclusion criteria applied to the control group Each subject included in the study signed a consent form. Only five women refused to be interviewed: three in the experimental group and two in the control group and they are not considered further.

Each woman was interviewed during postpartum stay in hospital, on average 3 days after delivery. The study continued for 5 months, by which time 40 women with low-birthweight babies had been recruited to each of the two categories; those with a gestation <37 weeks (preterm group) and those who had SGA infant, defined as a birthweight <10th centile according to the standards defined by Thomson *et al.* (1968). All women had gestational age assessed at about 16 weeks by an ultrasound scan.

Life events were measured for 12 months before the delivery, using the Life Events and Difficulties Schedule (LEDS) (Brown & Harris 1978). The interviewer (TM) was trained by the group at Bedford College and audio-taped early interviews to ensure that the schedule was being used correctly. The interview first established the nature and extent of the woman's social network, then asked about a list of possible events. Each question was followed by a series of supplementary probing questions to check if a possible event fulfilled previously defined inclusion criteria. If so, the full details were elicited so that the degree of objective threat or unpleasantness could be rated. Thus, a husband being off work through illness would only be included as an event if the illness had lasted at least 4 weeks or clear evidence of financial hardship was present. The objective degree of threat would depend on the likelihood of gaining immediate further employment, the financial circumstances of the family and the amount of sick pay.

The rating of objective threat was not made by the interviewer but by a group of experienced raters who did not know whether the woman was in the experimental or control group. The objective circumstances of the event together with the woman's life circumstances at the time were described by the interviewer, without reference to the woman's subjective response. The group then rated the threat on a four point scale and this report will only be concerned with events rated as 'severe' in the long-term. Such severe events include bereavement, marital separation and severe illness or imprisonment of a close family member. In addition to discrete life events, the LEDS assesses ongoing chronic difficulties which were rated in the same way.

Events and difficulties that were associated with the pregnancy (e.g., hospital admissions due to threatened miscarriage or pre-eclampsia) were excluded from the analysis.

Social support was assessed using the intimacy scale of the LEDS. The highest point on this scale (A) indicates a close confiding relationship with husband or cohabitee—this is described for the purpose of the present report as the presence of good social support. Lower points (B–D) indicate the lack of such a relationship with husband/cohabitee whether or not there is a confiding relationship with another relative or friend. For the purpose of the present report these lower points were combined as the absence of good social support.

Psychiatric status was measured using the Present State Examination (PSE) (Wing *et al.* 1972) and concerned any psychiatric symptoms that had been consistently present for the 4 weeks up to the delivery. The CATEGO computer programme was used to provide an index of definition; those at index of definition level 5 or above being classified as 'cases' of psychiatric disorder.

Social class was based on the Registrar General's classification using husband's occupation for married women and current or last occupation for single women; unemployed women living with parents were rated according to the main bread winner. Cigarette smoking was recorded and alcohol consumption was measured in units of alcohol consumed per week. The latter used the four question modified MAST score (Michegan Alcoholism Screening Test) described by Selzer (1971).

Obstetric factors were taken from the case notes: previous obstetric history, pregnancy complications of vaginal bleeding and hypertension.

Statistical analysis used the χ^2 test to compare differences between the three experimental groups and the controls. Multivariate analysis used a binomial-logit model (Royal Statistical Society 1986).

Results

Overall 184 mothers were interviewed, of these 92 had low-birthweight babies and 12 women had preterm babies which were also SGA (<10th centile) (Thomson *et al.* 1968); the results for these will be described separately. The mothers will be considered in four groups.

Preterm group. Birthweight <2500 g, but of appropriate weight for gestational age and born before 37 weeks gestation ($n = 40$).

Mixed group. Birthweight <2500 g, SGA and born before 37 weeks gestation ($n = 12$).

SGA group. Birthweight <2500 g, SGA and born after 37 weeks gestation ($n = 40$).

Control group. Birthweight >2500 g and born after 37 weeks gestation ($n = 92$).

There were no significant differences (χ^2 test) between the low birthweight and control groups according to the following demographic variables; age, marital status, ethnic group, height, employment status of subject/husband, social class, proportion receiving supplementary benefits, sex of child, number of planned pregnancies. In addition there were no significant differences between the low birthweight and control groups according to level of education of mother, free milk, use of antenatal clinics, and use of parentcraft classes. The principal differences between the four groups are shown in Table 1.

Table 1. Number of subjects in each group positive for each of the principal variables.

Variable	Low birthweight groups (n = 92) 1 (n = 40)	 2 (n = 12)	 3 (n = 40)	Control group 4 (n = 92)
Smoking (any amount)	20	6	26*	35
Bleeding during pregnancy	10*	2	3	2
Previous low birthweight baby	8*	0	9*	2
No. with severe life event or difficulty				
Throughout pregnancy	31*	8	30*	48
During 3rd trimester	7	0	14*	14
No. without good social support	19	7	30*	35
Psychiatric disorder	10	3	13	17

*Significant difference ($P<0{\cdot}05$) between the low-birthweight and control groups

Multivariate analysis

In order to assess the relative effects of the different variables a binomial-logit model was used with backward elimination of non-significant variables (Royal Statistical Society 1986). Such an analysis yields those variables which are independently and significantly associated with low birthweight.

The following variables were included as present or absent: supplementary benefits, previous pregnancy, previous low-birthweight baby, good social support, severe event and/or difficulty at any time during pregnancy, (and in separate analysis: severe event in last trimester), psychiatric disorder, hypertension, bleeding during pregnancy. Smoking during pregnancy was rated on a three point scale—none, up to 20 cigarettes, more than 20 per day. Alcohol consumption was similarly rated—none, up to 10 units and >10 units per week.

The first analyses compared all the low-birthweight groups (groups 1, 2 & 3) with the control group so that our results can be compared with previous similar studies. The variables that emerged as significant were: previous low-birthweight baby ($P<0{\cdot}001$); severe event and/or difficulty ($P<0{\cdot}001$); bleeding during pregnancy ($P<0{\cdot}001$)

Thus for the total group of mothers the experience of a severe event or marked continuing difficulty was significantly related to low birthweight *after* allowance for the effect of a previous low-birthweight baby and bleeding during pregnancy Because only those who have had previous pregnancy could have had a previous low birthweight baby this analysis was repeated excluding primaparae. The findings were similar. When the analysis was repeated comparing group 1 (preterm births, n = 40) with the control group, the same three variables emerged as significant.

Comparing group 2 (preterm and SGA, n = 12) with the control group yielded three variables as significant: smoking, alcohol consumption and bleeding during pregnancy, but the best model emerged with the two variables; pregnancy bleeding ($P<0{\cdot}05$) and alcohol consumption (>10 units/week) ($P<0{\cdot}025$).

Comparing group 3 (SGA, n = 40) with the control group yielded the following variables as significant: previous low-birthweight baby ($P<0{\cdot}005$); low social support ($P<0{\cdot}001$); smoking (any quantity) ($P<0{\cdot}01$).

Since group 2 is so small the results for this group alone must be treated with caution. The analysis was first performed for each of the three groups separately so that the results for 'pure' preterm and 'pure' SGA groups could be ascertained The analyses were repeated with the 12 subjects of group 2 added to each of the other groups in turn. The results for these enlarged groups of preterm births and SGA babies remained the same. For both groups a previous low-birthweight baby was a significant factor; for the preterm group bleeding during pregnancy and severe event/chronic difficulty were additional factors, for the SGA group the additional factors were lack of good social support and smoking

Discussion

The design of this project differed from other studies in several important respects. The present study investigated low-birthweight babies as a separate group whereas Brooke *et al.* (1989) and Stein (1987) studied birthweight as a continuous variable; they found no relation between overall birthweight and life events during pregnancy. Brooke *et al.* (1989) recognized that their results could not be extrapolated to a separate group of low-birthweight babies.

The present study was similar to that of Newton & Hunt (1984), who identified a small number of low-birthweight babies among consecutive deliveries and, like us, found that mothers of these low-birthweight babies had experienced more objective major life events during pregnancy. However, Newton & Hunt (1984) investigated 18 low-birthweight babies, and our study included 90 low-birthweight babies The larger number of low birthweight babies was the result of the case control design used in the present study. This meant that there were sufficient numbers to analyse the preterm and SGA births separately, which has not been done previously.

There were two further differences. No previous study has used the detailed method of life event measurement (LEDS), which has known reliability in collection of retrospective data. Finally, the present study, like that of Newton & Hunt (1984) was performed in a deprived inner city area where social conditions are quite different from those studied by Stein *et al.* (1987) and Brooke *et al.* (1989).

The different results in these four studies might be attributable either to the difference in design or the different geographical locations. It is notable that Stein *et al.* (1987) did not include detailed obstetric data in their analyses and Brooke *et al.* (1989) did not examine gestational age.

Although there is some overall similarity between the present findings and those of Newton & Hunt (1984) they are not identical. We found that the obstetric factor of a previous low-birthweight baby emerged as an important predictor of low birthweight, a finding reported in longitudinal studies (Bakketeig *et al.* 1979). In addition, as anticipated, bleeding in pregnancy was a significant predictor of low birthweight and preterm delivery. Even after these two factors had been accounted for there was a further significant effect attributable to severe life events/chronic difficulties during pregnancy for the preterm group. Whereas Newton & Hunt (1984) found an effect of events and difficulties during the last trimester, the present study found the effect was related to severe life events and difficulties throughout pregnancy. This was a surprising finding since an increase in catecholamine excretion, associated with social stress during the last trimester, has been postulated as a trigger of preterm labour (Bentekoe *et al.* 1977).

In the SGA group, smoking was significantly associated with low birthweight, and this was independent of the significant effects of a previous low-birthweight baby and lack of social support. This result is important. Others have found that once the effect of smoking is taken into account the effect of social variables disappears (Morrison *et al.* 1989; Brooke *et al.* 1989) leading to the conclusion that 'provision of social support is not in itself likely to improve outcome in terms of fetal growth' (Brooke *et al.* 1989). Such a view negates the rationale for preventive research (Spencer *et al.* 1989, Oakley 1989) but our results suggest that at least in Central Manchester there may be a direct effect from lack of social support.

It has been suggested that current social conditions in an inner London borough during the 1980s are unlikely to lead to the nutritional deficiencies and chronic infections that may have explained the previous link between social class and birthweight (Brooke *et al.* 1989). However, it is clear that social conditions have differed considerably between studies. In Oxford the proportion of single mothers was 6·5% (Stein *et al.* 1987) compared with 20% in the present study and the rates of psychiatric disorder were 6% and 23% respectively. The percentage of births <2500 g was 3% in the Oxford sample compared with 10% in Manchester (Central Manchester Health Authority 1988).

In the inner London study (Brooke *et al.* 1989), 12% of women belonged to social classes IV and V, compared with 51% of the present sample. The proportions receiving supplementary benefits were 8·2% and 35·8% respectively. The proportion of women reporting no confidant (no-one with whom they can discuss freely all their concerns) was 5·4% in the London study and 32% in the present sample. The term 'lack of social support' may therefore have a different meaning in the deprived social conditions of the present study than in the more middle class areas of the London and Oxford.

A possible mechanism for the relation

between social stress and low birthweight has been proposed by Picone *et al.* (1982a, b). They found that stress reduced efficiency of calorie utilization leading to reduced maternal weight gain (in spite of maintained calorie intake) and reduced placental weight. They postulated that increased catecholamine excretion might cause this reduced utilisation of calories. Since social support may protect women from the deleterious effect of social stress (Brown & Harris 1978), lack of good social support may be the key factor leading to reduced intrauterine growth.

Picone *et al* (1982a, b) observed that smoking was similarly associated with reduced maternal weight gain and low birthweight but *without* a reduced placental weight. This provides a possible explanation for the findings of the present study. Lack of social support and smoking, though both related to reduced intrauterine growth, may involve different mechanisms, only the former involving reduced placental weight.

Our finding that both smoking and reduced social support were independently related to the birth of SGA infants lends strong support to the suggestion by Oakley (1985 and 1989) that help with stopping smoking should be offered to pregnant women along with additional support. But such help would best be offered only to those women whose social situation was very deprived, of whom there were a considerable number in the present study.

Like Stein *et al.* (1987) we found that the presence of psychiatric disorder did not emerge from the multivariate analysis as a significant factor that predicted low birthweight. Thus improvement in the psychological well-being of the mother (Spencer *et al.* 1989; Oakley 1989), while a worthwhile aim in itself, would not be expected to have a significant effect on infant birthweight.

This study has suggested that different mechanisms are involved in the link between social stress, smoking and low birthweight babies and should generate more specific hypotheses that can be tested in intervention studies. To date such studies have examined a global effect of improving social support which is possibly why they have demonstrated relatively little effect on birthweight (Spencer *et al.* 1989, Oakley *et al.* 1990).

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Comparison of the T/QRS ratio of the fetal electrocardiogram and the fetal heart rate during labour and the relation of these variables to condition at delivery

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Summary. The T/QRS ratio of the fetal electrocardiogram (ECG) was recorded to within 30 min of delivery from 105 women in labour. There were no significant differences in the mean T/QRS ratio in the last hour of record between those with normal and intermediate, or abnormal fetal heart rate (FHR) patterns. In 66 labours the mean T/QRS ratio in the first hour of record was compared with that of the last hour; the only significant change was a small decrease in the mean ratio from 11% to 7% in a group of 11 fetuses with an abnormal FHR pattern throughout the recording time. Eight babies were born with evidence of acidosis (umbilical artery pH$\leq$7·16), and another four were born in poor condition (1 min Apgar score <4) without evidence of acidosis; none had a mean last hour T/QRS ratio significantly different from the previously established normal range.

The need for improved intrapartum monitoring is clear, both to avoid unnecessary intervention, and to indicate accurately the need for delivery when fetal condition is compromised by labour. A normal fetal heart rate (FHR) is highly predictive of a good outcome (Schifrin & Dame 1972); however, an abnormal FHR alone is a poor predictor of fetal condition at delivery (Sykes *et al.* 1983). It has been suggested that analysis of the ST segment of the fetal electrocardiogram (ECG) may provide a better indication of fetal compromise than FHR analysis alone. Elevation of the T wave of the fetal ECG has been related to abnormal FHR patterns (Pardi *et al.* 1974, Lilja *et al.* 1985; Rosen *et al.* 1989) and to fetal acidosis (Jenkins *et al.* 1986; Rosen *et al.* 1989).

We have previously studied ECG recordings in 25 normal labours observing minute by minute changes in the T/QRS ratio (Newbold *et al.* 1989); the overall mean T/QRS ratio was 10% (SD 5%, range 4–23%). In each recording the T/QRS ratio varied around the mean (5th–95th centile range 13%) but did not change significantly as labour progressed. This suggests that each fetus has its own mean around which it shows little variation under normal conditions, and that changes from this may be significant. In this study, fetal ECG data are presented from 62 labours with FHR abnormalities and compared with 43 labours with normal FHR patterns; both ECG and FHR data are related to condition at delivery.

The pH of the umbilical artery is commonly used as an end point in studies of the fetal ECG

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because of the association between an elevated T/QRS ratio and fetal anaerobic metabolism which is well reported in animals (Rosen & Isaksson 1976, Hokegard *et al.* 1981). However, a decrease in fetal pH may also be caused by hypercapnaemia or by an infusion acidosis from the mother. To allow for these possibilities measurements of blood gases and base deficit (BD) were obtained in addition to the pH from the umbilical artery (Ua) and vein. The maternal status was assessed from the base deficit of maternal venous blood (Mv). The lower limit of normal for cord artery blood pH is known to vary between centres. A recent sample ($n = 250$) from our own population has been used as a standard for this study. The findings were: mean umbilical artery pH 7·24 (SD 0·08), $P\mathrm{co}_2$ 7·3 (SD 1·4) kPa, base deficit of 6·4 (SD 2·9) mmol/l and mean delta base deficit (Ua BD−Mv BD) −0·1 (SD 2·6) mmol/l. In this study the cord and maternal blood gas results of any infant with an umbilical artery pH of 7·16 or less were investigated to determine the origin of this acidosis.

Subjects and methods

The fetal ECG was recorded from 174 women requiring FHR monitoring during labour; 52% were monitored electively because they were 'high risk' pregnancies and 48% because of problems developing during labour. Signals were collected using a single re-usable Copeland fetal scalp electrode (Surgicraft, Redditch, UK) with the standard maternal thigh plate as a reference. The FHR was recorded using the standard labour ward monitor (Sonicaid FM3R, Sonicaid, Chichester, UK), the ECG signals were retrieved from the back of this monitor, and stored on magnetic tape (Racal 'Store 4' FM tape recorder) and analysed off-line. The recording and analysis systems have been described previously (Newbold *et al.* 1989). This work was approved by the hospital ethics committee, and informed consent was obtained for the additional ECG monitoring; patient management was independent of the ECG recording.

Recordings were included in the study only if the fetal ECG was recorded for at least 60 min and to within 30 min of delivery (19 recordings were excluded on these criteria). An additional 16 were excluded because of technical problems with the recording equipment or because blood samples were not collected at delivery. Thus recordings from 139 labours were available for analysis. In these the average T/QRS ratio was recorded for each minute, provided that at least 15 individual measurements were made during that minute (Newbold *et al.* 1989). A further 34 recordings, 25% of those available, were excluded because of poor data quality (ECG measurements were available from <30 min of the last hour of the record).

In the remaining 105 recordings, varying in duration from 63 to 852 min (median 216 min), the FHR pattern was analysed retrospectively in 30-min epochs (without knowledge of the T/QRS ratio) and each epoch was graded as normal, intermediate or abnormal (Table 1). The relation of the T/QRS ratio to the FHR pattern was assessed on an hourly basis, the FHR pattern being allocated to the more serious FHR grade if the two 30-min analyses were not the same. The delay between discontinuing the fetal ECG recording and delivery ranged between 1

Table 1. FHR pattern classification To be classified as normal an epoch had to satisfy all criteria of normality, any abnormal characteristic was sufficient to classify an epoch as intermediate or abnormal

Normal

Basal heart rate 110–150 bpm
Variability 5–25 bpm over 30 min
No late or variable decelerations
Early decelerations in the first stage of labour for short periods only (<30 min)

Intermediate

Persistent early decelerations >30 min first stage
Decreased beat-to-beat variability >30 min
Baseline bradycardia, 100–110 bpm >30 min
Baseline tachycardia, 150–170 bpm >30 min
Single episode bradycardia, but FHR remaining >100 bpm, and maximum duration 3 min
Maximum of 3 late or variable decelerations
Maximum of 3 decelerations of any type with slow recovery
Excessive variability >30 minutes

Abnormal

Persistent late decelerations
Persistent variable decelerations
Baseline tachycardia, >170 bpm>30 min
Single episode of bradycardia, with FHR <100 bpm, or >3 min duration
Complicated bradycardia
Complicated tachycardia
Complicated loss of variability

bpm = beats/min

and 30 min (median 5 min), 88% were delivered within 15 min of the end of recording. There were 67 normal vaginal deliveries, 32 operative vaginal deliveries and six caesarean sections in the study group. Of the operative deliveries 14 were expedited for 'fetal distress'. The condition of the infant at delivery was assessed by 1 and 5-min Apgar scores, and from measurements of acid-base and blood gases in the umbilical artery (Corning 178 blood gas analyser). Allowance for maternal acidosis was made by measuring the base deficit in maternal venous blood collected from the antecubital vein, typically within 5 min of delivery, and comparing this with the base deficit of the umbilical artery. In addition whole blood lactate levels (Roche 640 lactate analyser) were measured from 59 mothers and babies. There were no stillbirths or neonatal deaths.

The FHR pattern and the mean T/QRS ratio of the fetal ECG were compared over the last hour of the 105 records. In 43 there was a normal FHR pattern, in 18 an intermediate pattern and in 44 an abnormal pattern. The outcomes, and last hour T/QRS ratios, in the intermediate and abnormal FHR groups were compared independently with those in the normal group using either the Mann-Whitney *U*-test (with Yates' correction) or the χ^2 test.

Trends in the T/QRS ratio as labour progressed were studied by comparing the mean T/QRS ratio in the first and last hour of the recording. Twenty-seven recordings were excluded as they were of <120 min duration. A further 12 were excluded because changes in the FHR pattern did not show a persistent trend, leaving 66 recordings where comparisons could be made. Recording times varied from 123 to 852 min (median 252 min). Of these, 20 showed a normal FHR pattern throughout the whole record, 11 showed persistently abnormal FHR patterns, and the remaining 35 developed FHR abnormalities with the progress of labour. The FHR pattern changed from normal to intermediate in 10, from normal to abnormal in 17, and from intermediate to abnormal in eight of the labour recordings. Changes in the mean T/QRS ratio between the first and last hour of record in each of the five groups were compared using Wilcoxon's signed rank test.

Results

The group of 44 fetuses with an abnormal FHR pattern in the last hour of record (Table 2) showed statistically significant differences in all the measurements of acid base and blood gases at delivery when compared with the normal group ($n = 43$); these differences were not seen between the intermediate FHR group ($n = 18$) and the normal group. There were significantly more deliveries expedited for 'fetal distress' in the abnormal FHR group, but this difference was not found between the intermediate FHR group and the normal group. There were no significant differences in 1 and 5-min Apgar scores between the three groups. There were no significant differences in the mean T/QRS ratios for the last hour between the three FHR groups There was no significant correlation between the mean T/QRS ratio of the last hour and the pH or lactate concentration in the umbilical artery. A significant decrease (4%) in the mean T/QRS ratio between the first and last hour of record was seen in those with an abnormal FHR pattern throughout the whole record; no significant changes were seen in the other groups.

Eight of the 105 babies were born with an umbilical artery pH $\leq 7 \cdot 16$. In seven of these the last hour T/QRS ratio was within the normal range (Newbold *et al.* 1989) but in one the value was abnormally low (−5%); the significance of this is discussed below. Four other babies were born in poor condition (Apgar score <4 at 1 min) but without acidosis; in these records the mean T/QRS ratios for the last hour were also within the normal range. Cord and maternal blood results (Table 3) showed a primary metabolic acidosis in only three of the eight acidotic infants.

Discussion

The relation between the FHR pattern and fetal condition at birth found in this study confirms the clinical problem that although there is a correlation between an abnormal FHR and a decrease in fetal pH, the predictive value of the FHR is low This is reflected in the group of 44 fetuses with an abnormal FHR (Table 2). Twelve of this group (27%) required an operative delivery for suspected fetal distress but only 3 of the 12 infants were born with a low umbilical artery pH These findings on their own do not condemn FHR monitoring since if no action had been taken the condition at birth may have been more serious; however, they point to the requirement for a further system of fetal assessment. Fetal blood sampling was used in only

Table 2. Comparison of the T/QRS ratio and outcome at delivery in 105 labours grouped according to the FHR pattern in the last hour of record

	Normal FHR pattern	Intermediate FHR pattern	Abnormal FHR pattern
Number of subjects	43	18	44
T/QRS ratio (%)	8 (2–22)	8·5 (3–17)	7 (−5–19)
Normal delivery	35	13	19
Operative vaginal delivery	6	4	22
Caesarean section	2	1	3
Operative delivery for fetal distress	0	2	12*
Apgar score			
1-min	9 (3–9)	8 (3–9)	8 (1–9)
5-min	9 (5–10)	9 (8–10)	9 (2–10)
Umbilical artery			
pH	7·30 (7·16–7·39)	7·26 (7·16–7·38)	7·24§ (7·07–7·35)
$P\text{CO}_2$ (kPa)	6·95 (4·55–9·49)	7·53 (4·49–9·96)	7·40† (5·03–10·03)
$P\text{O}_2$ (kPa)	2·13 (0·89–3.29)	1·97 (0·65–3.65)	1·77† (0·91–3.57)
Base deficit (mmol/l)	4·3 (0·4–12·0)	4·9 (−0·6–9.8)	6·7‡ (2·1–10.4)
Lactate (mmol/l)	3·15 (1·53–7·01) (*n* = 20)	3·43 (2·22–5·24) (*n* = 11)	3·98† (1·72–7·55) (*n* = 28)
Delta base deficit (mmol/l)	−1.8 (−6·2–4·8) (*n* = 42)	−0·1 (−5·0–6·6)	+0·7§ (−4·9–5·3) (*n* = 43)

* $P<0{\cdot}05$ χ^2 test.
† $P<0{\cdot}05$. Mann-Whitney *U*-test (with Yates correction).
‡ $P<0{\cdot}01$. Mann-Whitney *U*-test (with Yates correction).
§ $P<0{\cdot}001$ Mann-Whitney *U*-test (with Yates correction)
Results are medians (range) values or numbers of subjects as appropriate.

seven fetuses in this study, six with an abnormal FHR pattern, and one with an intermediate pattern.

We had anticipated that some of the recordings with an abnormal FHR would have shown an increase in the T/QRS ratio. Lilja *et al.* (1985) reported an increase in the T/QRS ratio when comparisons were made in a similar manner across three groups with increasingly severe FHR abnormalities; however, they also reported that T/QRS ratio changes were sometimes transient, so data selection may have influenced their results. As only three of the 105 infants in our study showed evidence of significant fetal metabolic acidosis (Table 3) our chances of finding significant T/QRS ratio

Table 3. Cord and maternal blood gases at delivery in infants with umbilical artery pH of 7·16 or less

Infant	Ua pH	Ua $P\text{CO}_2$ (kFa)	Ua BD (mmol/l)	Mv BD (mmol/l)	Ua lactate (mmol/l)	Principal origin of acidosis
1	7·16	9·96	5·0	7·3	4·15	C
2	7·16	8·07	9·3	9·5	–	I
3	7·16	7·10	12·0	7·2	–	M
4	7·14	8·94	8·9	8·2	7·55	C
5	7·14	9·58	6·9	5·7	4·45	C
6	7·13	8·62	10·4	6·8	4·92	M
7	7·13	9·87	7·2	7·8	–	C
8	7·07	10·03	10·4	5·1	6·60	M

C = Hypercapnaemia ($P\text{CO}_2>8{\cdot}7$ kPa). I = Infusion acidosis (delta BD≤2·5 mmol/l). M = Metabolic acidosis (delta BD>2·5 mmol/l). Ua = umbilical artery. BD = base deficit. Mv = maternal venous

changes may have been reduced. We have data from a further fetus with a profound metabolic acidosis (Ua pH 6·98, Ua BD 14·3 mmol/l, delta BD 9·70 mmol/l) who was excluded from the study because the data quality in the last hour of the record was poor. Data were obtained for 125 min to within 5 min of delivery; during this time the FHR showed a persistent tachycardia with variable decelerations. The mean T/QRS ratio was calculated every 15 min, where possible, and rose from 11% to 19% but remained within the normal range. It was possible to examine trends in the T/QRS ratio in 66 of our recordings. Surprisingly the only significant finding was a decrease in the ratio in those subjects with a persistently abnormal FHR. Jenkins *et al.* (1986) studied trends in the T/R ratio during labour finding an overall increase in 10 acidotic subjects (Ua pH <7·20); however, individually there were wide variations and three showed a marked decrease in T/R ratio from the start of the recording.

Animal studies indicate that T wave elevation occurs in the fetal ECG during anaerobic myocardial metabolism which in turn leads to lactate accumulation (Rosen & Isaksson 1976; Hokegard *et al.* 1981; Greene *et al.* 1982). If the same mechanism operates in the human fetus then T wave analysis should identify those fetuses compromised by labour. Studies on humans have been on relatively small numbers and the evidence remains weak. Lilja *et al.* (1985) found a weak correlation between the T/QRS ratio recorded within 30 min of delivery and the umbilical vein lactate. Rosen *et al.* (1989) found an elevated T/QRS ratio in 12 of 13 infants with an umbilical artery pH <7·15 at birth; however, analysis of the umbilical artery bicarbonate suggested that the acidosis was of a respiratory origin in 8 of the 13 infants. Murray (1986) found no correlation between ST segment or T wave elevation and umbilical artery pH at delivery. The use of cord pH alone as an end point gives rise to concern; for example our own data (Table 3) showed that only a minority (3 of 8) of the fetuses with a low pH in the umbilical artery had a primary fetal metabolic acidosis; four were ascribed to hypercapnaemia and two to an infusion acidosis.

The timing of the appearance of an abnormal T/QRS ratio is important if it is to be used in the management of labour and available data vary about this. Jenkins *et al.* (1986) showed that abnormal changes could be present for some hours in the first stage of labour. Rosen *et al.* (1989) also reported abnormal changes in 46 (28%) of 163 fetuses studied during the first stage; only 7 of the 46 recordings with an abnormal T/QRS ratio were associated with acidotic infants at delivery, a predictive value of 15%. Although the proponents of T/QRS ratio measurement have emphasised the shortcomings of FHR monitoring, it seems unlikely that the T/QRS ratio alone will be an adequate substitute.

The fetal ECG waveform, recorded from the fetal scalp, may be distorted by noise leading to erroneous measurements of the T/QRS ratio; it is therefore important that any measuring system indicates when the signal quality is too poor for reliable measurements. In the present study, each T/QRS ratio was measured independently and the average ratio for each minute calculated, if less than 15 T/QRS ratios were measured in a minute, because of noise distortion, no average was calculated (this system requires four ECG complexes to measure one T/QRS ratio, therefore with good quality data 30 measurements would be made per minute with an FHR of 120 bpm). Of the other fetal ECG monitors currently in use, the ST analyser (Lindecrantz 1983) employs a system of template matching of the QRS complex, followed by signal averaging of accepted complexes, provided an adequate number of complexes are accepted during a set time period. The Nottingham system (Kirk & Smith 1986) employs time coherent weighted averaging to produce a stable baseline before any measurements are made; if the signal to noise ratio is poor (<6) then the data are considered to be unsuitable for analysis.

Of the 105 satisfactory full recordings in our series two had negative T/QRS ratios in the last hour; examination of the original signals showed that both had flat or very small T waves (positive or negative) during this hour. However, the complexes were unusual in that substantial parts of the complex, starting at the PR segment, were depressed relative to the pre-P region so that the QRS complex occurred at a depressed level (Fig. 1). Murray (1986) reported that PR segment depression was commonly seen during labour and did not correspond to any specific acid-base status. As the system used in this study set the iso-electric line from the pre-P region the peak of the small T wave occurred below the iso-electric line and was measured as negative. We have been able to replay the same data through

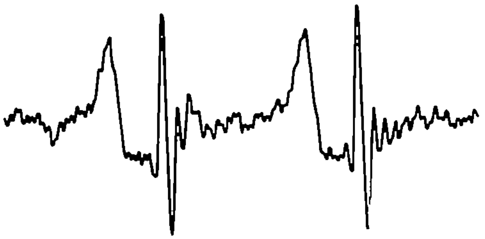

Fig. 1. ECG signals showing prominent P waves with depression of the PR segment and QRS complex relative to the pre-P region.

both the fetal ECG monitor currently in use at Nottingham and the ST analyser. The Nottingham system recorded similar T/QRS measurements to our own. The ST analyser recorded slightly higher T/QRS values because the 'isoelectric' line is set from the PR segment by that system. This may explain the higher 'normal' T/QRS ratio of 15% (SD 5%) recorded on the ST analyser (Lilja *et al.* 1988) than that of 10% (SD 5%) found in our study of normal subjects (Newbold *et al.* 1989).

In conclusion, we have failed to demonstrate that abnormal T/QRS ratios were associated with four fetuses with defined metabolic acidosis at birth; nor have we found a relation between abnormal FHR patterns and the T/QRS ratio. The relatively small numbers will not make this a conclusive study; however, we now intend to investigate short-term changes in the T/QRS ratio in relation to uterine contractions and also the significance of the PR:RR interval correlation, which has been shown to be associated with fetal acidosis at delivery (Murray 1986).

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Peritoneal fluid volume and sex steroids in the pre-ovulatory period in mild endometriosis

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Summary. Twenty infertile women with laparoscopically confirmed mild endometriosis and ten women with tubal infertility underwent diagnostic laparoscopy 32 h after the onset of the endogenous luteinizing hormone (LH) surge during a spontaneous menstrual cycle. All visible peritoneal fluid was aspirated for assessment of volume and sex steroid content. There was no significant difference in peritoneal fluid volume or concentrations of oestradiol, progesterone and androstenedione between the two groups. Furthermore in the endometriosis group there was no significant difference in peritoneal fluid volume and concentrations of sex steroids between those women who had been treated previously with danazol and those who were left untreated.

The peritoneal fluid environment has been recognized as a dynamic zone of gamete interaction that may be of relevance in early study of sperm and oocyte transport, fertilization and early embryo cleavage (Syrop & Halme 1986). Although the origins of peritoneal fluid are not completely understood, it appears not to arise as a result of tubal secretory activity (Koninckx *et al.* 1980). Maathuis *et al.* (1978) have suggested two mechanisms of origin. The first is a change in vascular permeability effected by oestradiol at the level of peritoneal membranes, and the second is the ovarian-peritoneal transfer of fluid, around the time of follicular rupture. It seems likely that both mechanisms are important and that peritoneal fluid volume depends mainly on follicular activity, corpus luteum vascularity and hormonal production (Bouckaert *et al.* 1986, Syrop & Halme 1987a). In addition, however, certain pathological conditions such as endometriosis have been associated with alterations in volume, although the literature here is inconsistent (Mahmood & Templeton 1990).

Similarly the levels of sex steroids in the peritoneal fluid are influenced by ovarian activity (Maathuis *et al*, 1978, Donnez *et al.* 1982) and rise to a maximum following ovulation (Zorn *et al*, 1982; Melega *et al.* 1984), although Kruitwagen *et al.* (1987) did not report significant difference in peritoneal fluid oestradiol levels between the pre-ovulatory and post-ovulatory periods.

The purpose of this study was to assess peritoneal fluid volume and sex steroid concentrations in women with mild endometriosis during a spontaneous cycle at a defined time during the immediate pre-ovulatory period. Women with tubal infertility acted as controls.

Subjects and methods

The study included 30 women. The first group (study group) included 20 women with primary infertility who had minimal to mild endometriosis diagnosed at an earlier diagnostic laparoscopy Endometriosis was graded according to the classification developed by The American

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Fertility Society (1985); the median AFS score was 7 (range 2–10). The median age of the women was 29 years (range 22–34 years) and the median duration of infertility 5·5 years (range 3·5–7·5 years) all had ovulatory midluteal phase serum progesterone concentrations of >30 nmol/l and they all had a normal prolactin levels (<600 IU/l) during at least two consecutive cycles Ten of these 20 women had been treated previously with danazol (600 mg daily for 6 months) and the remaining ten were left untreated. Each woman had one laparoscopy during this study. The median interval between the two laparoscopies was 16 months (range 14–20 months) in the danazol-treated group and 12 months (range 10–15 months) in the untreated group. The median AFS score at the second laparoscopy was similar in the two groups: 8 (range 4–10) in the treated group and 6 (range 2–10) in the untreated group.

The second group who acted as controls included ten women with primary infertility due to bilateral tubal occlusion. Their median age was 31 years (range 24–35 years) and the median duration of infertility 5 years (range 3–7 years). They also had ovulatory midluteal phase serum progesterone levels of >30 nmol/l and normal serum prolactin levels as described above. These ten women had had 12 laparoscopies during the study (two women had two laparoscopies).

Study design

The women were scanned daily (Diasonic DRF 200 with 7·5 MHz vaginal probe, Diasonic Sonotron, Bedford, Bedfordshire) from day 5 of the menstrual cycle. Blood levels of oestradiol, progesterone and luteinizing hormone (LH) were assessed daily until a dominant follicle emerged measuring >16 mm; then blood samples were taken every 6 h for assay of LH. The first LH value that exceeded 180% of the mean value of the previous four samples was taken to indicate the onset of the LH surge (Testart *et al.* 1981; Messinis *et al.* 1985). Laparoscopy was performed between 30 and 34 h (mean 32 h) after the onset of LH surge, using a triple puncture technique (Renou *et al.* 1986). At the laparoscopy, all the visible peritoneal fluid from the pouch of Douglas and anterior utero-vesical reflection was aspirated. After the volume was assessed, the peritoneal fluid was then transferred into lithium heparin tubes, kept at room temperature and centrifuged within 2 h at 2000 rpm/h for 10 min. The supernatant fluid was aspirated with pasteur pipettes and stored at −40°C in lithium heparin tubes. One woman in the endometriosis group had already ovulated and in another woman, peritoneal fluid was contaminated with ham's media and was discarded. In the control group, no visible fluid could be aspirated in one woman because of the obliteration of the pouch of Douglas.

Hormone assays

Blood LH was measured by monoclonal antibodies in an immunoradiometric assay (IRMA) (Serono Diagnostics, Ltd, Surrey, UK) and the results expressed as mIU/ml of standards of human pituitary LH (WHO 1st IRP 68/40). The sensitivity of the assay was 1·8 mIU/ml. Inter- and intra-assay co-efficients of variation were 7·9% and 6% respectively.

Oestradiol in peritoneal fluid was measured by a radioimmunoassay kit (RIA) purchased from Diagnostic Products Corporation, Los Angeles, CA. Sensitivity of the assay was 80 pmol/l, while inter- and intra-assay co-efficients of variation were between 5·4% and 9% and 5% and 8% respectively.

Progesterone in peritoneal fluid was measured by a RIA kit purchased from Amersham (Amerlex-M Progesterone RIA kit). Sensitivity of the assay was 1·3 nmol/l and inter- and intra-assay co-efficients of variation were between 6% and 7% and 10% and 11% respectively.

Androstenedione in peritoneal fluid was measured in a RIA kit (coat-a-count) Diagnostic Products Corporation. The sensitivity of the assay was 0·02 ng/ml and inter- and intra-assay co-efficient of variation were between 7% and 10% and 4% and 7% respectively.

Statistical analysis

Results were analysed using the statistical package or Minitab (Statistical Department, Pennsylvania University, PA) Levels of periteonal fluid volume, oestradiol, progesterone and androstenedione were compared using unpaired *t*-tests.

Results

Of the 20 laparoscopies in the endometriosis group,. 18 samples of peritoneal fluid volume were available for steroid assessment. For the ten women in the tubal infertility group, nine samples of peritoneal fluid were available for analysis.

There were no significant differences between the two groups in mean peritoneal fluid volume, and levels of oestradiol, progesterone and androstenedione (Table 1).

Furthermore in the endometriosis group there was no significant difference in peritoneal fluid volume and sex steroid levels between those women who had been treated previously with danazol and those who were left untreated (Table 2).

Discussion

Published information on peritoneal fluid volume in patients with endometriosis is inconsistent Significant elevation has been reported throughout the menstrual cycle (Koninckx *et al.* 1980; Badawy *et al.* 1985; De Loen *et al.* 1986; Fisk & Tan, 1988; Moretuzzo *et al.* 1988) or only in the early secretory phase (Oak *et al.* 1985; Bouckaert *et al.* 1986) although others could not confirm increased volumes (Rock *et al.* 1982; Olive *et al.* 1985). These reports did not investigate periovulatory peritoneal fluid volumes which may be more relevant in relation to the endocrine environment of the developing oocyte. Rezai *et al.* (1987) did not find a significant difference in peritoneal fluid volume in the periovulatory phase between women with mild disease (mean 17·4 ml SEM 3·3) and a control group (mean 13·0 ml, SEM 1·7). However, the laparoscopies were performed between days 13 and 18 of the menstrual cycle without pinpointing ovulation and it is possible that some of these patients might have ovulated when laparoscopies were undertaken. This would certainly explain the high peritoneal fluid volumes Devroey *et al.* (1985) reported the pre-ovulatory endocrine profile of peritoneal fluid in a group of five women with unexplained infertility, but did not report on actual volume.

This is the first study, therefore, where laparoscopy was performed in the immediate pre-ovulatory period. The mean peritoneal fluid volume in women with mild endometriosis was not significantly higher than that in women with tubal infertility. Furthermore peritoneal fluid volume was not affected by previous medical treatment. It could be argued that women with tubal infertility are not the ideal control group because the presence of pelvic adhesions may affect the collection of peritoneal fluid. However, in this study only one patient had evidence of partial obliteration of the pouch of Douglas and no fluid could be aspirated. In the remaining women, infertility was related to problems of oocyte pick-up and there was no evidence of adhesions in the pouch of Douglas.

The endocrine milieu of the peritoneal fluid may be of importance in the genesis of endometriosis. Brosens *et al.* (1978) and Koninckx *et al.* (1980) postulated that low levels of progesterone in the peritoneal fluid of women with endometriosis during the luteal phase may be more conducive to the development of endometriosis by favouring implantation of endometrial cells

Table 1. Peritoneal fluid volume,* oestradiol, progesterone and androstenedione in women with mild endometriosis and those with tubal infertility

Variables	Study group (endometriosis) (*n* = 18) Mean (SEM)	Control group (tubal infertility) (*n* = 9) Mean (SEM)
Fluid volume (ml)	7 6 (1·04)	6·9 (1·60)
Oestradiol (pmol/l)	787 (116)	894 (268)
Progesterone (nmol/l)	7·44 (1·06)	8·14 (1·68)
Androstenedione (nmol/l)	7·83 (1·05)	7·22 (0·89)

* Pouch of Douglas and uterovesical reflection.

There are no significant differences between the two groups

Table 2. Effect of treatment with danazol on peritoneal fluid volume and sex steroid levels in women with minimal-mild endometriosis

	Treated endometriosis-group (*n* = 9) Mean (SEM)	Untreated endometriosis-group (*n* = 9) Mean (SEM)
Peritoneal fluid volume (ml)	6·3 (0·84)	7·6 (1·04)
Oestradiol (pmol/l)	915 (207)	673 (120)
Progesterone (nmol/l)	8·75 (1·98)	6·30 (0·92)
Androstenedione (nmol/l)	8·60 (1·93)	7·83 (1·05)

There are no significant differences between the two groups.

arising from retrograde menstruation (Sampson 1940; Ridley 1968). But it can be argued that these floating endometrial cells would not be capable of survival for a long period because of the presence of actively phagocytizing macrophages in the peritoneal fluid (Syrop & Halme 1987b). Although we are unable to report on steroid levels in the luteal phase comparable levels of progesterone in peritoneal fluid were noted in the periovulatory phase in both study groups. Walmer & Haney (1988) suggested that the peritoneal fluid endocrinology merely reflected ovarian function.

Our results show that peritoneal fluid volume in women with mild endometriosis is not significantly different from that in women with tubal infertility and the ovarian functional contribution towards the endocrine milieu in the peritoneal fluid in the pre-ovulatory phase is similar in the two groups. Furthermore sex steroid levels are not affected by previous medical treatment.

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The free-flap vaginoplasty; a new surgical procedure for the treatment of vaginal agenesis

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Summary. The ideal operation for a young woman born without a vagina would be a one stage procedure, creating a functionally normal vagina without cosmetically unattractive scars, without the need for subsequent dilatation, stents or obturators. This goal was achieved with a free flap vaginoplasty using a full thickness skin graft taken from the scapula region. The blood supply of the graft was maintained by microvascular anastomosis of the graft pedicles to vessels in the groin. The operation has been performed in three young women who were born with uterine hypoplasia and vaginal agenesis. We experienced no unexpected complications, the procedure was well tolerated and left our patients with a good length, fully functional vagina. However, the operation is a major undertaking and needs to be performed by those with expertise in plastic surgery as well as in gynaecology.

Surgeons have devised many ingenious operative procedures which create a vagina for women born without one (Johnson & Lilford 1990). However, they all have disadvantages. The ideal operation would provide a vagina that is of good length, does not need to be dilatated, will not cicatrize nor stenose, does not mutilate the vulva and does not leave an ugly donor site. To avoid constriction and contraction the surgically created recto-vesical cavity (potential neo-vagina) needs to be lined with a full thickness tissue flap with an integral blood supply. Bowel flaps have been used for the purpose but skin has many advantages. An epithelial skin lining avoids the need for intra-abdominal surgery and is not associated with a mucous discharge or an unsightly introitus. Myocutaneous pedicle skin flaps from the medial aspect of the thigh have a precarious blood supply (Mathes & Nahai 1984) and flaps taken from the abdominal wall involving rectus abdominus (Lilford *et al.* 1989) are very bulky and can only be transposed after extensive pelvic dissection behind the bladder. To avoid these complications we decided to use a free skin graft. We describe the first cases of vaginal agenesis treated with a free flap graft consisting of full thickness skin obtained from a scapular site.

Patients and methods

All three patients had congenital uterine hypoplasia and vaginal agenesis; (Rokitansky syndrome; Hauser & Schreiner 1961). They were aged between 17 and 19 and formed part of a group of patients who did not want to practise self dilatation. They were offered a choice between the McIndoe procedure (McIndoe & Bannister 1938), tissue expansion vaginoplasty (Lilford *et al.* 1988) and the free flap operation.

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They were aware of the experimental nature of this surgery and that it would be a lengthy and major operation.

The free flap vaginoplasty is a single operation involving four stages.

Stage 1

Under anaesthesia the patient is placed in the lithotomy position, draped and swabbed and an inverted u-shape incision is made over the dimple of the Müllerian pit. A recto-vesical cavity is created by blunt finger dissection making a space that will accommodate the length of two fingers. The mid-line sagittal fibrous septum may have to be divided with scissors at the top of the neo-vagina. Venous bleeding responds to tamponade.

Stage 2

The patient is then positioned supine and the right groin cleansed and draped (for the right handed surgeon). A 5 cm skin incision is made one finger breadth below the inguinal ligament in the line of the skin crease, exposing the femoral vessels. A long and wide calibre vein and an artery with few branches, originating close to the femoral vessels, are identified and mobilized from their distal attachments (usually the superficial femoral circumflex vessels suffice). Once sufficient vessel length has been obtained to avoid tension at the future anastomosis with the graft vessels, the distal end is clipped temporarily. The vessels from the graft will be passed under a skin bridge in the groin to meet the mobilized femoral branches. This sub-cutaneous tunnel is created at this stage by blunt dissection starting at the medial edge of the groin incision to emerge at the perineal incision.

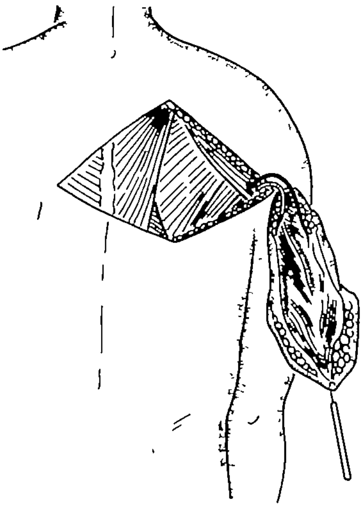

Fig. 1. Raising a free skin flap from the back. The circumflex scapular vascular pedicle is mobilized back as far as the axillary artery

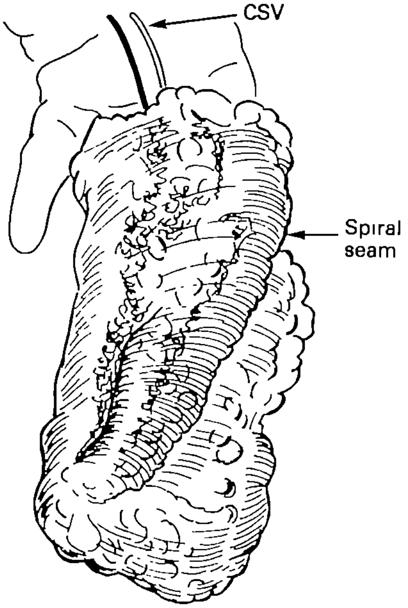

Fig. 2. Making a pouch from the skin flap. The skin is innermost and the pouch is closed at the medial end to become the vault of the neo-vagina The lateral aspect of the flap will become the introitus supplied by the circumflex scapular vessels (CSV).

The wound is then temporarily closed and the patient turned on her left side.

Stage 3

A free skin flap is raised from the back overlying the scapula using the technique of Mayou *et al.* (1982) (Figure 1). This vascular pedicle is mobilized to its origin at the axillary artery and the vessels are divided as close as possible to the axilla. Haemostasis is secured and the donor site closed over a drain. The *in-vitro* skin flap measures 18 cm from left to right and 10 cm from top to bottom corner. It is trimmed of excess fat and fashioned into a pouch that will form the new vagina (Figure 2). The seam is spiralled and the pouch is closed at the opposite end from the origin of the vascular pedicle. The opening of the pouch is fashioned into an oval extending obliquely into a beak at the site of the seam. The patient is then placed in the Lloyd-Davis position.

Stage 4

Only the right groin and the vaginal introitus are exposed. The neo-vaginal pouch, skin innermost, is then placed into the rectovesical cavity. The vascular pedicle is directed towards the right, the vaginal pouch is checked to ensure that it is not twisted and then the opening is secured to the introitus. To prevent an annular scar at the site of the anastomosis the apex of the original inverted u incision is extended posteriorly and mediolaterally to create a small Y-plasty that accommodates the beak of the pouch. The vascular pedicle is tunneled underneath the subcutaneous bridge in the groin to emerge in the inguinal wound (Figure 3). The patient is then positioned supine and the groin wound is reopened. Using microvascular surgical techniques, the previously mobilised branches of the femoral vessels are anastomosed to those supplying the neo-vagina. The groin incision is then closed.

Post-operative care

The recto-vesical cavity is drained with closed system suction drainage and the bladder drained suprapubically until the patient can micturate comfortably.

Post-operatively they are nursed with their thighs flexed and extension is forbidden Subcutaneous heparin is used to minimize thrombosis but prophylactic antibiotics are not used.

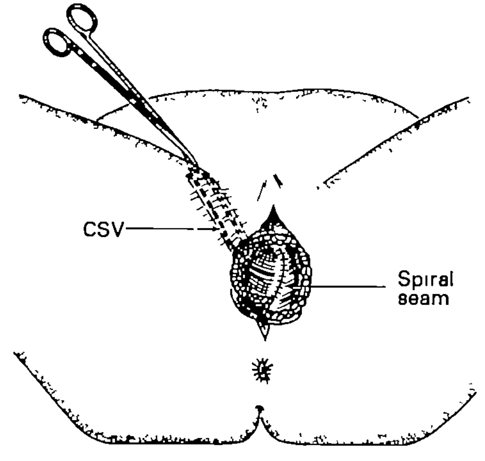

Fig. 3. The neo-vaginal pouch is placed into the recto-vesical cavity and the circumflex scapular vessels (CSV) are passed under the skin bridge and anastomosed to vessels in the groin.

Results

Three young women with vaginal agenesis have been treated with a free flap vaginoplasty. They knew that the procedure was experimental but were keen to avoid the two stage vaginoplasty and did not want to be subjected to self-dilatation that is invariably required with the McIndoe procedure. Post-operatively, the tissue perfusion of the first patient was monitored with a reflectance pulse oximeter. After 20 min a pulsatile signal was obtained which corresponded to the patient's heart rate and the oxygen saturation recorded by the oximeter was 94%. The signal strength was poor and post-operative monitoring was not continued. Apart from post-operative pyrexia that lasted for 48 h, there were no complications. The first patient has returned to another country and is reported to be enjoying coitus and claims to be asymptomatic. The second and third cases have also had excellent results. The vaginal introitus appears quite normal. Both of the remaining patients have vaginas of at least 4 inches in length (it is possible to reach the vault by digital examination) but the second patient has a rather tight stenotic ring at the site of the introital anastomosis.

This will admit one, but not two fingers, and may require a Z-plasty before intercourse can begin. The last patient has no such narrowing and claims to be enjoying intercourse.

Discussion

The large number of surgical procedures (Johnson & Lilford 1990) that can be offered to a woman born with vaginal agenesis is a tribute to the operator's ingenuity and imagination but it implies that the perfect operation has yet to be described. The classical treatment of repeated self dilatation (Frank 1938) and the bicycle seat modification (Ingram, 1981) are tedious and rarely achieve a full length vagina if the woman has no more than a Mullerian dimple. Williams' pouch (Williams 1964 & 1970) leaves the young woman with a short and abnormally angled vagina. The alternative to a pseudo-vagina is to create a neo-vagina by surgically opening the recto-vesical space. This space has to be lined to prevent adhesion of the vaginal walls. Split skin (Abbe 1899, McIndoe & Bannister 1938), full thickness skin, peritoneum (Tamaya *et al.* 1984), amnion (Dhall 1984) gut supplied by a vascular pedicle, devitalized gut and even rabbit gut have all been used (Cairns & De Villiers, 1980). Unfortunately none of these linings is ideal. Amnion cannot be used nowadays because of the fear of transmitting AIDS. Our current knowledge of heterografts prevents us repeating the work described by Ciriechieke in 1892 (see Cairns & De Villiers, 1980) with rabbit gut. Split skin grafts create a neo-vagina that will contract unless persistent regular dilatation is carried out. Contraction and stenosis and the need for obturators, moulds and dilators can best be avoided by lining the recto-vesical space with viable tissue carrying its own blood supply. A segment of interrupted bowel with its mesentry can be transposed into the recto-vesical space. This major procedure can leave the patient with an ugly stoma at the introitus that looks like a colostomy and through which mucosa may prolapse. The alternative to pedicle bowel grafts is a full thickness skin flap taken from the perineum (Wee & Joseph 1989, Song *et al.* 1982), thigh (McGraw *et al.* 1976), buttock, abdomen (Lilford *et al.* 1989; Tobin & Day, 1988; McGraw *et al.* 1988) or skin that has been newly created using tissue expansion techniques (Lilford *et al.* 1988). Perineal flaps limit the length of the potential vagina and mutilate the vulva, flaps from gracilis, the buttock or the groin have a notoriously precarious blood supply and leave the woman with long thigh, buttock or groin scars. Skin from the abdomen involves major surgery and encroaches upon the integrity of the abdominal wall. Tissue expansion techniques can create sufficient labial skin to line a neo-vagina but this involves a two-stage procedure with prolonged hospitalisation A free graft has the potential advantages of offering a young woman with no vagina a one stage operation to create a functional anatomically normal vagina. It is suitable for young women with vaginal agenesis (with or without uterine hypoplasia) and for women who have lost their vagina following radiotherapy or surgery for vaginal cancer. It lines a recto-vesical cavity with full thickness skin, sparing the patient the tedium of self dilatation and limiting the risk of contraction. The potential donor site is not limited by its distance from the pelvis and can be selected to be cosmetically unobtrusive.

In our experience, the free flap vaginoplasty fulfills all of these promises. However, the operation is a major undertaking. The viability of any free flap can never be guaranteed and the women are left with three wounds instead of one. The procedure involves a four stage operation; the creation of a recto-vaginal space, mobilizing adequate donor vessels, isolating a graft and making it into a vaginal pouch and finally placing the pouch into the recto-vesical space and uniting the vessels supplying the pouch to those in the groin. The potential complications are related to each stage. In general the woman is at risk of thrombosis associated with any major pelvic surgery which takes over 3 h. The first stage may be complicated by venous haemorrhage from the pelvic venous plexus or by perforation of the rectum or bladder. The first will respond to tamponade and the second should only occur as a result of surgical mishap. The second stage involves exposing the femoral vessels and puts the patient at risk of deep venous thrombosis. However, this risk is probably no more than theoretical and will not be greater than the similar risk associated with a long saphenous ligation employed for the treatment of varicose veins. The complication of the third stage depends upon the chosen site of donor skin. Isolating skin with sufficient vessel length from over the scapula involves dissection close to the axillary vessels and nerves with potential of causing damage to either of these structures. The risks and complications of the final stage include leakage and subsequent groin haematoma from the microsurgical anastomosis. Insufficient vessel length may necessitate vein interposition graft, thus increasing the risk of graft failure and subsequent necrosis and infection. Failure of the microsurgical anastomosis would be difficult to detect especially as ischaemia would initially develop at the vault. Although others (Salova & Horton, 1988) have claimed that devitalized full thickness skin can safely be left in the recto-vesical space, the potential risk of infection from a mass of dead tissue between the rectum and bladder must, in our opinion, limit such management.

Urinary infection from the catheter, which must be left *in situ* until the introital oedema has subsided, must be considered to be a minor but common complication of any vaginoplasty. Other potential complications associated with poor technique may include introital stenosis or a perineal hood. Late complications will be related to changes in the new vagina. Dysplasia and even carcinoma have been reported in skin transplanted into the vagina and there is no reason to assume that a free flap would not have the potential to be similarly afflicted. As the new vaginal skin has associated adipose tissue, obesity may be associated with increased fat deposition around the vagina, limiting the potential space for the bladder, ureters and even the rectum. The increasing bulk of the graft may cause displacement of the ureter with consequent obstruction, particularly as the ureters may be abnormally positioned.

Finally, the vagina will be dry and if the donor skin originates from the hair-bearing area then there may be discharge associated with the hair follicles.

Whilst in theory a free flap vaginoplasty has much to recommend it, and in our experience the operation fulfilled our expectations, the procedure is a major surgical undertaking lasting over 3 h with significant potential risks. The advantages it offers over other techniques must be offset against these disadvantages. In our opinion it should be limited to women who want a one stage operation to create a fully functional and cosmetically normal vagina without the restrictions of self dilatation. Women with a sizeable Mullerian pit should be offered dilatation with or without Ingram's moulds. Obstruction of the lower vagina (with haematacolpos) should be treated using a perineal skin flap (Wee & Joseph, 1989). Young women with total vaginal agenesis and the mental fortitude to withstand tissue expansion should be offered Lilford's tissue expansion vaginoplasty and those who live in regions of the world without expertise in vaginoplasty or plastic surgery should be offered either a Williams' vulvovaginoplasty or a bowel transplant.

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Repeated measurement of maternal weight during pregnancy. Is this a useful practice?

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Summary. A retrospective study of 1092 pregnant women showed that the use of a centile chart of maternal weight gain was not effective at detecting women who give birth to small for gestational age (SGA) infants. Multiple regression analysis showed that of the various weight measurements recorded, weekly weight gain and maternal size at booking were the only factors which had a significant association with infant birthweight after taking into account maternal gestation, age, smoking habit and parity. Low maternal booking weight (< 51 kg) was the most effective maternal weight measurement for antenatal detection of SGA infants (positive predictive value 20·0%). Low average weekly maternal weight gain (< 0·20 kg) had a positive predictive value of only 12·9% for detecting these pregnancies. Weight loss or failure to gain weight over a 2-week interval occurring in the third trimester was observed in 46% of all women studied. Maternal smoking had a positive predictive value of 16·3% in antenatal detection of SGA infants. Maternal weight need be recorded only at booking, with the exception of patients in whom nutrition is of concern. The subsequent routine weighing of patients may produce unnecessary anxiety and should cease.

Small for gestational age (SGA) and low birthweight (LBW) infants contribute to a major proportion of perinatal deaths and childhood morbidity and the antenatal identification of these infants remains a priority for antenatal care.

Maternal weight gain has been estimated routinely in antenatal clinics since 1941 (Scott & Benjamin 1948) when it was introduced to monitor maternal nutrition. There is little evidence that maternal weight gain is an effective antenatal screening test for SGA infants (Gordon e
al. 1978; Elder *et al.* 1970) although studies hav
shown a positive association between materna
weight gain and infant birthweight (Beilly &
Kurland, 1945; Thomson & Billewicz 1957
Nyirjesy *et al.* 1968; Singer *et al.* 1968; Niswander *et al* 1969; Simpson *et al.* 1975; Miller *et a*
1976, Rosso & Luke 1978; Harrison *et al* 198
Luke *et al.* 1981, Ounsted & Scott 1984)

In this study we have examined systematicall
pregnancy outcome and complications i
relation to the extremes of maternal weight and its change throughout pregnancy. First, we have explored the effectiveness of using a centile chart of maternal weight gain in detecting women who subsequently give birth to SGA infants. Second, we have examined the booking weight, weight gain between 28 and 36 weeks, and average weekly weight gain over the whole pregnancy and the association between these

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measures and infant weight allowing for gestation, maternal age, smoking and parity. Third, we have examined the association between excess maternal weight gain and hypertension.

Subjects and methods

The study population ($n = 2580$) was derived from women delivered in the John Radcliffe Hospital in Oxford during a 12-month study period who gave addresses in areas from where more than 85% of the population are delivered in the John Radcliffe Hospital. From this population every alternate patient ($n = 1290$) was entered into the study. The maternal socio-demographic characteristics, details of the course of the pregnancy, and its outcome were obtained retrospectively from hospital records and general practitioner co-operation cards. The data were entered onto the Oxford University computer twice and an edit program was used to screen for errors in data collection and entry.

Maternal weight gain was calculated by subtracting weight at the booking visit from all weights recorded during pregnancy. Small-for-gestational age was defined as a birthweight < 10th centile for gestational age and sex in normal pregnancies based on standards derived from women delivered in Oxford (Yudkin *et al.* 1987). The scales used for weighing patients were predominantly beam and spring balances. The validation of these scales has been described previously (Dawes & Grudzinskas 1991).

The data from 198 of the 1290 women were not included for analysis to produce the centile chart as there was no record of infant sex or birthweight, or fewer than three weights recorded during pregnancy. The mean number of clinic attendances after booking with weight recorded was 8·4 (SD 3·6).

The average weight gain between 28 and 32 weeks, 32 and 36 weeks, and 28 and 36 weeks was calculated as was average weekly weight gain. The weekly rate of maternal weight gain was computed by dividing the total weight gain by the number of weeks between booking and the gestation at which the last weight was recorded.

The body mass index (BMI) was calculated from the formula weight/height^2 (kg/m^2). The Central Oxford Research Ethics Committee approved the study.

Results

There were 507 primigravidae, and in 1035 pregnancy lasted between 37 and 41 weeks. The 10th, 50th and 90th centiles of maternal weight gain of 988 women booked before 20 weeks and delivered between 37 and 41 weeks were calculated for each gestational week from week 10 to week 40.

There was a very large range of maternal weight gain in the 103 women who gave birth to SGA infants (Fig. 1) The proportion of women (booking before 16 weeks) who had SGA infants was not statistically significantly different between the group of women whose weight gain was < 10th centile at any time between 20 and 40 weeks gestation and the group whose weight gain never fell below the 10th centile. The sensitivity, specificity, positive and negative predictive values of using the test 'maternal weight gain falling below the 10th centile between 20 and 40 weeks gestation in women booking before 16 weeks' to detect women subsequently giving birth to SGA infants was 19.4%, 87.1%, 12.7%, 91.8% respectively.

The correlation coefficient between total weight gain and infant weight was 0·026. The correlation coefficient between infant birthweight and maternal variables were calculated (Table 1). To determine whether maternal weight gain contributed to the variation of birthweight independently of gestation, maternal age, parity, and smoking habits, we performed a stepwise multiple linear regression analysis in which the measurements of weight gain were entered after these variables. Stepwise regression was performed with all variables included in the model and then removing each non significant variable at a time until only variables that were significant predictors of birthweight were

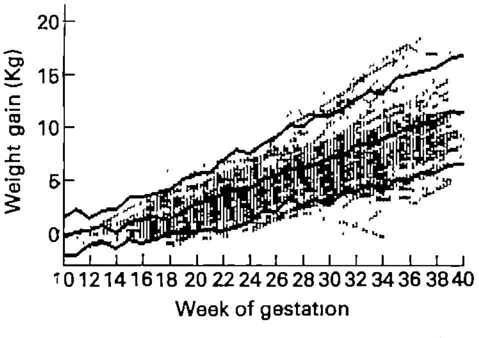

Fig. 1. Maternal weight gain in women ($n = 103$) who gave birth to small-for-gestational age (SGA) infants Superimposed are the 10th, 50th and 90th centiles of 988 women who booked before 20 weeks, and were delivered between 37 and 41 weeks gestation.

Table 1. Correlation coefficient between infant birthweight and maternal variables

	Mean	(SD)	Correlation coefficient
Birthweight (kg)	3·32	(0·60)	
Gestational age (weeks)	39·5	(2·52)	0·56
Maternal age (years)	26·6	(5·1)	0·06
Parity	0·86	(1·0)	0·10
Smoking	3·23	(6·5)	−0·15
Booking weight (kg)	63·1	(11·3)	0·23
BMI	24·3	(4·1)	0·15
Average weekly weight gain for total pregnancy (kg)	0·38	(0·15)	0·20
Average weekly weight change (kg) between:			
28–32 weeks	0·41	(0·32)	0·08
32–36 weeks	0·48	(0·38)	0·15
28–36 weeks	0·46	(0·29)	0·20

included. Average weekly weight gain, BMI and booking weight were the only weight related variables that were left after this analysis (Table 2). Low booking weight, low average weekly weight gain and low booking BMI were all assessed as screening tests to determine women at risk of having SGA infants (Table 3).

The frequency of raised blood pressure (BP > 140/90 on one occasion) was statistically significantly higher in those women whose maternal weight gain exceeded the 90th centile for maternal weight gain between 10 and 40 weeks ($n = 236$, 16%) than in women whose weight gain was not greater than the 90th centile ($n = 855$, 10%, $P < 0{\cdot}05$). There was, however, a large variation in weight gain in women with high blood pressure (Fig. 2). The sensitivity, specificity, and predictive value of a positive and negative result of the screening test (maternal weight gain rising above the 90th centile between 20 and 40 weeks gestation in women booking before 16 weeks) was 26%, 80%, 15%, and 89% respectively.

The 10th centile of maternal weight gain was also assessed as a screening test for women who subsequently give birth to infants with low Apgar scores ($\leqslant 4$) or infants requiring admission to a special care baby unit. The sensitivities of this test for these conditions were 16% and 21% respectively with positive predictive values of 4% and 5% respectively.

In women who smoked at all during pregnancy ($n = 269$, 16·4%) the frequency of SGA infants was statistically significantly higher than in women who did not smoke ($n = 828$, 7·1%) ($P < 0{\cdot}001$). There was no statistically significant difference in maternal booking weight between smokers and non-smokers but smokers were statistically significantly younger ($P < 0{\cdot}001$). Smoking was assessed as a predic-

Table 2. Prediction of birthweight: stepwise multiple linear regression analysis

Step	Variable entered	Partial R^2	Model R^2	B (partial regression coefficient)	F Statistic	Prob > F
1	Gestation	0·271	0·271	0·116	309·6	< 0·001
2	Weight	0·039	0·31	0·019	29·8	< 0·001
3	Weekly weight gain	0·026	0·336	0·593	26·3	< 0·001
4	Age	0·016	0·352	0·009	6·5	< 0·02
5	Smoking	0·007	0·359	−0·040	9·7	< 0·01
6	BMI	0·007	0·366	−0·028	7·8	< 0·01
7	Parity	0·006	0·372	0·059	9·9	< 0·01

Table 3. Low booking weight, average weekly gain, and low BMI at booking as predictors of SGA infants

	Sensitivity	Specificity	Predictive Value +VE test	Predictive Value −VE test
Booking weight < 51 kg	21.3%	92.1%	20.0%	80.0%
Average weekly weight gain < 0.20 kg	12.9%	91.3%	11.8%	88.2%
Booking BMI < 20	13.8%	90.4%	13.9%	86.1%

tor of SGA for gestational age infants. The sensitivity, specificity, predictive value of a positive and negative result were 43%, 93%, 16%, and 77% respectively.

Discussion

Since the report from the Medical Officer of Health in 1929 suggested that pregnant women should attend antenatal clinics at 16, 24 and 28 weeks gestation, then every 2 weeks until 36 weeks and weekly thereafter until delivery, the pattern of antenatal care in this country has remained the same. The routine weighing to monitor the nutrition of all pregnant women was begun in antenatal clinics in London in 1941 (Scott & Benjamin 1948). Although maternal nutrition remains an important element of antenatal care the antenatal detection of SGA or low birthweight babies has become one of the priorities in antenatal care (Gordon 1977). Despite the research describing the association of maternal weight gain and fetal growth, the effectiveness of routine measurement of maternal weight gain to detect women at risk of having a growth retarded fetus remains unclear (Thomson & Billewicz 1957, Singer *et al.* 1968, Elder *et al.* 1970, Gordon *et al.* 1978, Rosso 1985, Abrams & Laros 1986, Lawton *et al.* 1988).

We have confirmed that weight gain was positively association with infant birthweight but that the correlation was low. Our findings are similar to those found by Rosso (1985) and Abrams & Laros (1986) but less than that found in earlier work (Nyirjesy *et al.* 1968, Simpson 1975). We have also confirmed that the major determinants of birthweight, after taking into consideration gestational age, were maternal size at booking, maternal weight gain and maternal age but that these only accounted for 9% of the variation in infant birthweight.

The higher prevalence of SGA infants born to women with low weight gain reflected this association, but examination of the value of the centile chart of maternal weight gain in screening for SGA infants indicates that this is not an effective test. In fact the centile chart only meets two of the criteria set down for a screening test (Grant & Mohide 1982), namely that it is cheap and acceptable.

Multiple regression analysis showed that the weight changes occurring between 28 and 32, 32 and 36 and 28 and 36 weeks were not significantly associated with infant weight after taking into account gestation, maternal age, smoking and parity. By comparison, booking weight, booking BMI, average weekly weight gain did have a significant effect on infant birthweight. The sensitivity of using low average weekly weight gain to detect women at risk of having SGA infants was considerably lower (12.9%) compared with booking weight (21.3%). Our findings confirm those by Elder *et al.* (1970) that the increased prevalence of SGA infants is associated with weight loss or static weight in the third trimester, but that this has no practical predictive value. Weight loss or failure to gain weight over a 2-week interval in the third trimester was observed in 46% of all women studied.

The factor that had the highest association with weight gain was maternal booking weight

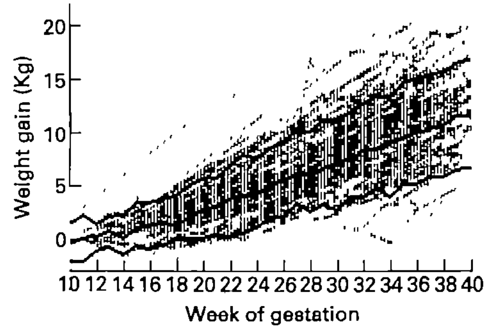

Fig. 2. Maternal weight gain in women ($n = 236$) found to have raised blood pressure during pregnancy. Superimposed are the 10th, 50th and 90th centiles of 988 women who booked before 20 weeks, and were delivered at between 37 and 41 weeks gestation.

(Peckham & Christiansen, 1971; Dawes & Grudzinskas 1991). It is likely that the results of maternal weight gain in detecting SGA infants were mostly due to the effect of booking weight on weight gain and we have shown that this factor was independently a better predictor of SGA infants than maternal weight gain.

The predictive values of booking weight for SGA infants were low compared with two ultrasound scans which have a negative predictive value of 99·6% and a positive predictive value of 28% (Neilson *et al.* 1984).

Maternal weight gain has been incorporated into multifactorial risk scores as a screening test for SGA infants with encouraging results (Cnattingius *et al.* 1985; Wennergren 1982). The most important factors for primigravidae were maternal smoking followed by symphysis-fundal height, and maternal weight before pregnancy. The weighted value of weight gain in these scoring systems is small.

Futhermore as the detection of oedema is no longer recommended as a diagnostic feature of pre-eclampsia (Nelson 1955) there is no argument for using weight gain to detect fluid increase.

Since the early 1940s body weight has achieved a prominent place on the antenatal record, next to blood pressure, but with little evidence to support its importance. The theory that maternal weight gain might predict infant weight is not supported by the evidence presented. Weighing generates anxiety in patients and requires as much explanation as any other screening procedure. The false assurance given to women who gain a 'normal' amount of weight is as wrong as the worry caused by 'low' or 'high' weight gain.

The woman who has a high or low weight at antenatal booking needs investigation for a possible organic or psychiatric cause. In the absence of either of these, referral to a dietician should be considered. The routine recording of maternal weight gain in pregnancy in women with a normal weight at booking should cease.

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Patterns of maternal weight gain in pregnancy

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Summary. A retrospective study of 1145 pregnant women showed that trends in mean maternal weight gain from the time of booking until delivery were not linear. Statistically significant lower rates of maternal weight gain were seen before 16 weeks, after 36 weeks and between 28 and 32 weeks gestation ($P<0\cdot05$). The mean maternal weight gain was 10·71 kg (SD 4·3) and the mean weekly weight gain was 0·38 kg (SD 0·16). A wide variation of maternal weight gain was seen in women with a normal outcome. The mean weight gain in heavy (>68 kg) and light (<55·4 kg) women was less than that in women whose weight was in the third quartile (60–68 kg, $P<0\cdot05$). The mean maternal weight gain was less in young (<20 years) women than in older women (>25 years; $P<0\cdot05$), less in parous than in primigravid women from week 37 onwards ($P<0\cdot05$), less in smokers than in non-smokers from 20 weeks onwards ($P<0\cdot05$), and greater in hypertensive women (BP>140/90) than in normotensive women ($P<0\cdot05$) from week 24 onwards. The mean weight gain in women who had small for gestational age (SGA) infants was not significantly different from that in women who had infants that were of appropriate size for gestational age. After taking into account infant and placental weight using multiple regression analysis, the factors that were associated with statistically significant differences in average weekly weight gain were parity, body mass index, smoking habit and raised blood pressure. Only 9·6% of the variation in average weekly weight gain could be predicted using these variables. It is unlikely that the measurement of maternal weight gain would be useful in detecting women who will have SGA infants or will develop hypertension.

The study of maternal weight gain in pregnancy has been confined mainly to total weight gain during the pregnancy. The pattern of maternal weight gain has been described only by few authors (Thomson & Billewicz 1957, Rosso 1985; Gregory & Rush 1987; Harrison *et al.* 1980). Total weight gain has been examined in relation to infant and maternal characteristics, but not systematically in relation to weight gain in normal pregnancy.

The dietary habits of the populations examined have changed since the first major studies were performed in the late 1940s and early 1950s when the diet of the participants in these studies was similar because of rationing (Scott & Benjamin 1948; Thomson & Billewicz 1957; Humphreys 1954). This is shown by the wide variation

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in both booking weight and weight gain seen in later studies compared with earlier work (Humphreys 1954; Abrams & Laros 1986).

In this study, patterns of maternal weight gain have been examined in relation to socio-demographic factors and pregnancy outcome, which include maternal social class, age, parity, height, booking weight, body mass index, smoking habits and blood pressure and infant sex, weight and frequency of small-for-gestational age infants.

Subjects and methods

The study population ($n = 2580$) was derived from women who were delivered in the John Radcliffe Hospital in Oxford during a 12-month study period and lived in areas from where >85% of the population are delivered in the John Radcliffe Hospital.

From this population every alternate patient ($n = 1290$) was entered into the study. The recommended number of visits for a woman during pregnancy in the United Kingdom is 12–13. The few data that are available indicate that this target is not often achieved (Hall & Chng 1982; Blondel 1985; Marsh 1985). The mean number of weights recorded for each woman was 9·4 (SD 3·6). No differences were found in maternal or infant measurements or outcome of pregnancy in women who had fewer than six or more than 12 weights recorded during pregnancy compared with women who had between six and 12 weights recorded.

The maternal socio-demographic characteristics, details of the pregnancy and outcome were obtained retrospectively from hospital records and general practitioner co-operation cards. The maternal records in Oxford classify social class as the occupation of the head of household in the following groups: self-employed, manager, foreman, employee, or retired. The data were entered onto the Oxford University Computer twice. An edit programme was used to screen for errors in data collection and entry. Maternal weight gain was calculated by subtracting weight at the booking visit from all weights recorded during pregnancy. Total pregnancy weight gain was estimated by subtracting the weight at booking from the last measured weight before delivery. The weekly rate of maternal weight gain was computed by dividing the total weight gain by the number of weeks between booking and the gestation at which the last weight was recorded.

The body mass index (BMI) was calculated from the formula weight/height^2 (kg/m^2). Small-for-gestational age (SGA) was defined as birthweight below the 10th centile for gestational age and sex in normal pregnancies based on standards derived from women delivered in Oxford (Yudkin *et al.* 1987). Pregnancy and its outcome was defined as normal if delivery occurred between 37 and 41 completed weeks gestation after booking before 20 weeks, and birth of a live infant with a birthweight between the 10th and 90th centiles for sex and gestational age (AGA). The scales used for weighing patients were predominantly beam and spring balances. To assess the accuracy and reproducibility of these scales, 15 scales were tested weighing the same person on the same day in the same clothing, with and without an 800 g weight. The mean of the 15 weighings was 72·05 kg (SD 0·12), and with the 800 g weight the mean of the 15 weighings was 72·83 kg (SD 0·12).

The significance of differences between means of average weekly weight gain over differing periods of gestation was analysed using the paired t-test. The multiple regression analysis was determined by using SAS stepwise forward multiple regression analysis. The statistical significance of different means of maternal weight gain or weight change observed was determined by Student's t-test. The normality of distribution of weight gain was calculated using the χ^2-test. The Central Oxford Research Ethics Committee approved the study.

Results

Means of maternal weight gain were calculated after allowing for the effect of gestation on maternal weight gain by only including the 988 women who booked before 20 weeks and gave birth at between 37 and 41 weeks (study group) (Table 1). These data were used to derive the range for mean weight gain throughout normal pregnancy summarized in Fig. 1. This shows a slight fall in rate of weight gain towards the end of the second trimester and at the end of pregnancy To examine this further, average weekly weight gain was calculated for six 4-week intervals 16–20, 20–24, 24–28, 28–32, 32–36, 36–40 weeks gestation, and from booking to 16 weeks gestation (Table 2). There was a significant increase in average weekly weight from before 16 weeks to the period 16–20 weeks ($P<0·001$). The average weekly weight gain between weeks

Table 1. Characteristics of the study group (n=988)

	Mean	(SD)
Booking weight (kg)	62·7	(11·15)
Height (cm)	162	(6·2)
Number of weights recorded	9·8	(3·2)
Maternal weight gain (kg)		
Total	10·71	(4·3)
Average weekly	0·38	(0·16)
Maternal age (years)	26·6	(5·1)
Gestation at delivery (weeks)	39·5	(1·7)
Birthweight (kg)	3·32	(0·54)

28 and 32 was significantly less than that seen between weeks 32 and 36 (P<0·05). The average weekly weight gain between weeks 36 to 40 was significantly less than that seen between 32 and 36 weeks (P<0·001). The mean weight gain observed from booking until delivery was 10·71 kg (SD 4·3). Maternal weight gain was found not to differ from a normal distribution at each of the gestational weeks examined. The mean maternal weight gain at week 36, of 525 women in the study group whose infants weighed >10th centile was 10·16 kg (SD 4·36) (Fig. 2).

The variation in mean maternal weight gain was examined at weeks 20, 24, 28, 32, 34, 36, 37, 38, 39, 40 in the 788 women who gave birth to AGA infants. Differences in mean maternal weight gain were not apparently associated with either social class, or sex of the newborn. The mean weight gain of taller women (>1·66 m) was greater than that of shorter women (1·62–1·66 m) only at weeks 24 (P<0·05) and 37 (P<0·01). The women whose booking weight was in the third quartile (60–68 kg) had the greatest mean weight gain at any gestation (11·6 kg at 38 weeks) compared with women of different booking weight. The lowest mean weight gain (10·3 kg at 38 weeks) was seen in women whose booking weight was in the highest quartile (>68 kg). There was no significant difference in mean weight gain at any gestation between women whose booking weight was in the lowest (<55·4 kg) or second (55·4–50 kg) quartiles. The mean weight gain of women with a BMI in the third quartile (23–26) was greater than that of women with a BMI in the highest quartile (>26) at weeks 24, 30, 32, 34, 36, 37, 38, and 39 (P<0·05). The mean weight gain of the women with a BMI in the highest quartile was less than that of the women with a BMI in the first or second quartiles (<23) at weeks 24, 30, 32 and 37 (P<0·05). The mean weight gain of women aged <20 years was consistently less than in older women until week 37 (P<0·05). At week 40 the mean weight gain of younger women was greater than that of older women (P<0·02). From week 37 to week 40 the mean weight gain in multigravid women (11·1 kg at 40 weeks) was less than that seen in primigravid women (12·6 kg at 40 weeks, P<0·05). The mean weight gain was greater in women who had heavier babies (3·4–3·7 kg) than in those who had smaller babies (<3·12 kg) (weight gain at 38 weeks 11·5 kg compared with 10·2 kg). This difference was statistically significant at all weeks studied except weeks 20, 24, 39 and 40 (P<0·05).

The mean weight gain of the 92 women who

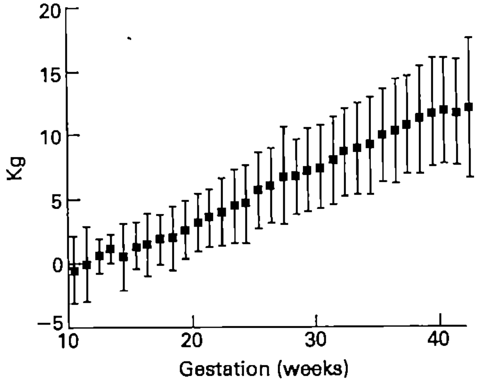

Fig. 1. Maternal weight gain in 988 apparently normal women with uneventful pregnancy and normal outcome at term in relation to gestational age (Mean ± 1SD).

Table 2. Average weekly weight gain in pregnant women for different gestational intervals from booking to 40 weeks gestation

Gestation interval (weeks)	Weight gain (kg) Mean	(SD)	n
Book to 16	0·31	(0·36)	
16–20	0·49	(0·34)	102*
20–24	0·50	(0·30)	98
24–28	0·47	(0·35)	122
28–32	0·43	(0·37)	99
32–36	0·49	(0·39)	145†
36–40	0·32	(0·41)	96‡

*Booking—16 weeks *vs* 16–20 weeks paired t-test <0·001.

†28–32 weeks *vs* 32–36 weeks paired t-test < 0·05.

‡32–36 weeks *vs* 36–40 weeks paired t-test <0·001.

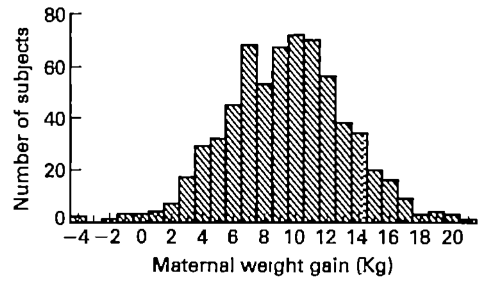

Fig. 2. The distribution of maternal weight gain from the time of booking (<20 weeks gestation) of 525 women at 36 weeks gestation who gave birth to infants with birthweights >10th centile at between 37 and 41 weeks gestation.

gave birth to SGA infants was less than that in the 788 women who gave birth to AGA infants at all weeks studied. These differences were not statistically significant (results not shown). The mean weight gain in women who gave birth to infants with birthweights >90th centile (12·5 kg at 38 weeks) was significantly greater at weeks 28, 30, 32, 36, 37, 38 and 39 than that seen in women whose infants were AGA (10·8 kg at 38 weeks) ($P<0{\cdot}05$) (Fig. 3). Of the 788 women with normal pregnancy outcome 182 were smokers at booking; 88 of them smoked more than ten cigarettes per day. The mean weight gain in women who smoked was significantly less than that in non-smokers ($P<0{\cdot}05$) for most of the weeks studied during pregnancy.

In 98 women who were found to be hypertensive (BP>140/90 mmHg) at any stage throughout pregnancy the mean weight gain was higher than that seen in normotensive women from weeks 28 to 40 ($P<0{\cdot}05$) except at weeks 30 and 37.

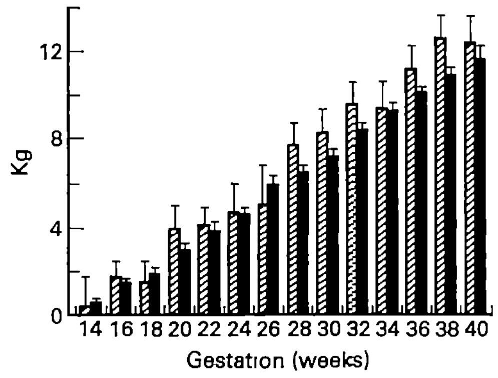

Fig. 3. Maternal weight gain by gestation in women who gave birth to infants with birthweights >90th centile ▨ and between the 10th and 90th centile ■ (Mean ± 2SE).

In the foregoing analyses it was probable that effects of other factors (i.e., infant weight) contributed to the differences in mean maternal weight gain seen. To control for this and other factors stepwise multiple regression analysis was performed. The objective of these analyses was to see whether, after allowing for infant weight and placental weight, the following factors affected average weekly weight gain; maternal height, booking weight, BMI, social class, civil state, age, parity, smoking habit, infant sex and hypertension. The average weekly weight gain over the total pregnancy was used so as to allow for the effect of time of booking on weight gain. The average weekly weight gain was modelled as the dependent variable and infant and placental weight were included as the first two variables. Multiple regression analysis was performed with all variables included in the model and then removing one variable at a time until only variables that were significant predictors of rate of weight gain were included (Table 3).

The range of R^2 for the whole model (i.e. using all the variables) indicated that these variables account for 10% of the variation seen in average weekly weight gain. The R^2 values indicate that infant weight accounts for only 3·4% of the variation of average weekly maternal weight gain. The value of B (partial regression coefficient) indicates that for each kg increase in infant weight there might be a 45 g increase in weekly average weight gain.

Parity also accounted for 3·4% of the variation in average weekly weight gain. For each previous pregnancy there was a 26 g decrease in average weekly weight gain. For each unit increase in BMI there was only a small decrease in weight gain (0·5 g). Hypertension was the only other factor having a significant positive effect on weight gain.

Discussion

The amount of maternal weight gain that is compatible with a normal outcome has been the matter of debate since the 1940s (Beilly & Kurland 1945; Thomson & Billewicz 1957; Hytten & Leitch 1971; Rosso 1985). The routine weighing of all pregnant women was begun in antenatal

Table 3. Prediction of average weekly weight gain: stepwise regression using forward selection

Step	Variable entered	Partial R^2	Model R^2	B (partial regression coefficient)	C(P) total of error^2	F	Prob>F statistic
1	Birthweight	0·034	0·034	0·045	44·6	27·4	<0·001
2	Placental weight	0·002	0·036	0·084	6·6	3·37	0·066
3	Parity	0·034	0·071	−0·026	22·4	27·9	<0·001
4	BMI	0·011	0·082	−0·005	14·9	9·4	<0·01
5	Raised BP	0·007	0·089	0·04	10·7	6·1	<0·05
6	Smoking	0·007	0·096	−0·01	7·0	5·7	<0·05

clinics in London in 1941 for the purpose of monitoring maternal nutrition (Scott & Benjamin 1948) and has been used since, without clear evidence of its effectiveness, as a screening test for maternal or fetal ill-health. The suggested importance of maternal weight gain in antenatal care has been demonstrated by its prominence on the antenatal card. Maternal weight gain is not only considered to be a significant clinical test but is also a measurement frequently discussed by the patient in consultation with the doctor or midwife. In spite of the perceived importance of this measure by both clinician and patient, it is remarkable that the available information from systematic research describing the pattern of normal weight gain is limited. Thomson & Billewicz (1957) described the weight gain curves of normotensive and hypertensive women, and Hytten & Leitch (1971) derived the components of weight gain at differing stages of pregnancy.

Our results expand the information available and for the first time since the end of rationing, describe the pattern of weight gain in pregnancies resulting in a retrospectively defined normal outcome in a homogeneous British population. Our data confirm previous findings that the maximum rate of weight gain is between 20 and 24 weeks gestation (Hytten & Leitch 1971). We have confirmed that there is a significant fall in rate of weight gain towards term in normal pregnancies and a slower rate of weight gain before 16 weeks.

By contrast with observations of Lawton *et al.* (1988), we did not observe a significant association between birthweight and maternal weight gain between 28 and 32 weeks gestation, although we did observe a statistically significant fall in rate of weight gain between 28 and 32 weeks in women with normal outcome.

The wide variation in maternal weight gain compatible with a normal outcome (i.e., 32 kg at 36 weeks) is larger than that reported previously (Hytten & Leitch 1971). This may be due in part to the large changes in dietary habits over the last 30 years and also the regional variations found in both booking weight and weight gain. Durnin *et al.* (1987) found the total weight gain in a population in Glasgow to be 11·7 kg (SD 3·2) which is more than in our study but the mean booking weight was 57·3 kg compared with a mean of 62·7 kg in Oxford.

Social class, and sex of the newborn had no significant effect on weight gain. The variation in maternal weight gain seen in women of differing height was significant only at 24 and 37 weeks. The booking weight has been shown to influence total weight gain (Beilly & Kurland 1945; Peckham & Christianson 1971; Simpson *et al.* 1975; Niswander *et al.* 1969; Luke *et al.* 1981). Our results showed that mean maternal weight gain was directly proportional to increasing maternal size until the 4th quartile when weight gain was lower than that of the women in the 1st quartile. This pattern was seen consistently from 24 weeks gestation. It is not clear if this lower weight gain in the very obese is a physiological response, or a reflection of dietary restriction.

The weight gain of young women was less than that seen in older women until week 37 when this pattern was reversed. The weight gain in parous women was less than in primigravidae from week 37.

The significant differences in weight gain were apparent in women of different size, age, and parity, but these differences may only explain 10% of the total variation in weight gain seen in normal pregnancy. The association of the total weight gain from booking to delivery with birthweight has been shown (correlation >0·99 to 0·18) by many authors using differing selection criteria (Thomson & Billewicz 1957; Beilly & Kurland 1945; Harrison *et al.* 1980; Simpson 1975; Niswander *et al.* 1969, Luke *et al.* 1981;

Nyirjesy *et al.* 1968; Singer *et al.* 1968; Miller *et al.* 1976; Rosso & Luke 1978; Ounsted & Scott 1984). Our results show a positive correlation between birthweight and maternal weight gain consistently from week 28, coinciding with the start of a steady rise in maternal tissue fluid (Hytten 1981; Hytten & Chamberlain 1980).

Women who smoke have a lower mean weight gain; the difference beween smokers and non-smokers was constant (1 kg) until week 36, the rate of mean weight gain in smokers declining thereafter. The difference in mean maternal weight gain at 40 weeks was 2·3 kg. These data confirm the findings of D'Souza *et al.* (1981), who studied 452 pregnancies in Manchester but contrast with the report of Anderson *et al.* (1984) who found the same maternal weight gain in smokers (12·8 kg) as in non-smokers (12·4 kg) in a series of 1975 Canadian women. Our findings have confirmed that smokers were younger, of a lower social class, booked later and had had more miscarriages and preterm deliveries and smaller babies. Furthermore, we have confirmed that women who smoke (>10 cigarettes per day) will give birth to smaller babies (mean birthweight difference 340 g; $P<0{\cdot}02$). This finding seems to be primarily a consequence of smoking given the independence of parity, BMI, booking weight and hypertension seen here. The weight gain in hypertensive women was greater than that in the normotensive in accordance with findings of Thomson & Billewicz (1957) who showed that in normotensives the maximum rate of weight gain was between 20 and 30 weeks whereas the rate of weight gain in hypertensive women increased as the pregnancy advanced.

Women having SGA infants gained less weight throughout pregnancy than women having AGA infants. The difference in weight gain was not statistically significant at any of the weeks studied. The women having large-for-gestational age infants had a greater mean weight gain from week 28 onwards except for week 34 and week 40 but there was no apparent difference in correlation between maternal weight gain and birthweight between women giving birth to AGA or large-for-gestational age infants.

The use of average weekly weight gain and multiple regression analysis identified four variables that were statistically significantly associated with maternal weight gain independently of infant and placental weight. Parity was the most significant factor but from analysis of means of weight gain this association becomes apparent only towards the end of pregnancy. Smoking produced a less significant association but was seen throughout pregnancy.

In clinical practice maternal weight is commonly used to identify women considered to be at risk of fetal compromise if weight gain is 'poor', or other disorders if weight gain is excessive. The variations in total weight gain and incremental weight gain seen here are so wide that these measurements are unlikely to be clinically useful. A systematic assessment is currently under way to determine the predictive value of abnormal weight patterns in specific abnormalities of pregnancy.

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Atrial natriuretic peptide and atrial size during normal pregnancy

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Summary. Plasma atrial natriuretic peptide (ANP), right and left atrial areas and the diameter of the left atrium were studied serially during normal pregnancy and at 6 weeks post partum in 21 nulliparous women. Concentrations of ANP in plasma were significantly elevated during mid-pregnancy. Thereafter ANP levels were not significantly different from those at 6 weeks after delivery. All atrial measurements were significantly increased in the third trimester of pregnancy, but none was significantly correlated with the plasma ANP concentrations. This might point at an altered mechanism of ANP secretion, which may be part of a physiological adaptive process to sustain the hypervolaemia of pregnancy.

Atrial natriuretic peptide (ANP), a peptide stored within granules in atrial cardiocytes, is known to be intimately involved in the control of fluid volume homeostasis (Needleman & Greenwald 1986). Its release is stimulated predominantly by atrial distension (Ledsome *et al.* 1985) as, for example, caused by intravascular volume expansion (Yamaji *et al.* 1985). Human pregnancy is characterized by an increase in circulating volume up to 50% more than non-pregnant values (Hytten 1985).

In the non-pregnant state, acute changes in circulating volume are known to be closely related in time to changes in both right and left atrial size and the concentration of ANP in plasma (Cannella 1988). Although many studies have reported elevated ANP levels during normal pregnancy (Cusson *et al.* 1985, Otsuki *et al.* 1987, Miyamoto *et al.* 1988, Thomsen *et al.* 1988, Jackson *et al.* 1988, Marlettini *et al.* 1989), the postulated links between the gradual gestational increase in intravascular volume, atrial stretch and ANP release have not been made clear. To our knowledge no data have been published on plasma ANP levels during pregnancy in relation to atrial size. We therefore measured plasma concentrations of ANP together with right and left atrial areas and the left atrial diameter serially during normal pregnancy.

Subjects and methods

The study included 21 healthy, nulliparous

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women who all gave informed consent. The experimental protocol was approved by the ethics committee of the university hospital. The mean age of the women was 25 years (range 19–33 years). They had uneventful, normotensive singleton pregnancies. In each woman, throughout pregnancy, diastolic blood pressure (Korotkoff, phase IV) in the sitting position was < 90 mmHg (Davey & MacGillivray 1988). Measurements were made serially at gestational weeks 14, 20, 28 and 36 and again 6 weeks post partum. Venous blood samples were taken after 15–30 min rest in the left lateral position.

Echocardiography

Echocardiographic examinations were made with the women in left lateral position after a period of 30 min of rest, using a Toshiba SSH–10A echocardiograph combined with a 2·25 MHz transducer. Right and left atrial area recordings were obtained by two-dimensional echocardiography by planimetry from the standard apical four-chamber view during end-systole. The left atrial transverse diameter during end-systole was measured by two dimensional as well as M-mode echocardiography from the standard parasternal long axis view. M-mode echocardiograms were recorded on a strip chart recorder at a paper speed of 100 mm/s. Final analysis of the recordings was performed off line from the cross-sectional echocardiograms recorded on videotape and from the M-mode echocardiograms using a digitising Kontron C–200 computer. For all indices, results are expressed as the mean value of five successive cardiac cycles.

In each woman serial blood sampling and echocardiography took place at the same time of day (inter-individual range, 13·00–17·00 h).

Determination of ANP

Blood was collected in EDTA-coated vacutainer tubes, immediately put on ice and centrifuged within 1 h at 4°C for 10 min at 1500 *g*. After adding 200 kIU aprotinin/ml (Trasylol, Bayer AG, Leverkusen, West Germany), plasma was stored in polystyrene tubes at -80°C until assayed. ANP was measured with a specific radioimmunoassay after extraction of the plasma on Sep-Pak C–18 columns (Rosmalen *et al.* 1987). Recovery of (99–126) hANP added to plasma was 96% and intra- and interassay coefficients of variation were 8·6 and 11·6% respectively. To minimize the effects of between assay variability, all samples from one patient were analyzed in the same assay run. Results are expressed as pg/ml

We have shown previously that the concentration of ANP in plasma during pregnancy is not affected by an enhanced degradation due to circulating enzymes from placental origin. The recovery of ANP in blood, after incubation of (99–126) hANP for 1 h at 37°C, was not significantly different between pregnant and non-pregnant women (Steegers *et al.* 1990).

Statistical analysis

Differences between the four measurements during pregnancy and the one obtained at 6 weeks post partum were analyzed by the Wilcoxon matched-pairs signed-ranks test. The level of significance for each comparison was taken to be 0·025. The total maximum type I error is then 0·10; however, due to the interdependency of the values at the subsequent time points, the actual type I error is probably nearer to 5% than to 10%.

Possible relations between ANP and atrial dimensions were assessed by determination of Pearson's coefficient of correlation (r) for the four pairs of observations for each woman during pregnancy. Then for each r the Fisher transform z was calculated, and for each pair of variables the weighted mean z_w was determined (Steel & Torrie 1984). For each pair of variables the k (k = number of women) individual correlation coefficients were tested for homogeneithy by calculating the weighted sum of squared deviations $\sum_i (n_i - 3)(z_i - z_w)^2$ and referring it to a X^2 table with k–1 degrees of freedom (Steel & Torrie 1984). In case of homogeneous correlation coefficients a pooled mean value of r and a 95% confidence interval (CI) were obtained by back converting z_w to r, with inclusion of an adjustment for bias (Steel & Torrie 1984). If the 95% CI does not include the value 0 the correlation coefficient is significant at the $P = 0{\cdot}05$ level.

Results

The results of the serial measurements of plasma ANP levels and atrial dimensions during pregnancy are shown in Fig. 1. Concentrations of ANP in plasma were significantly elevated at week 20, compared with 6 weeks after delivery. ANP levels at 28 and 36 weeks were not significantly different from those at 6 weeks post par-

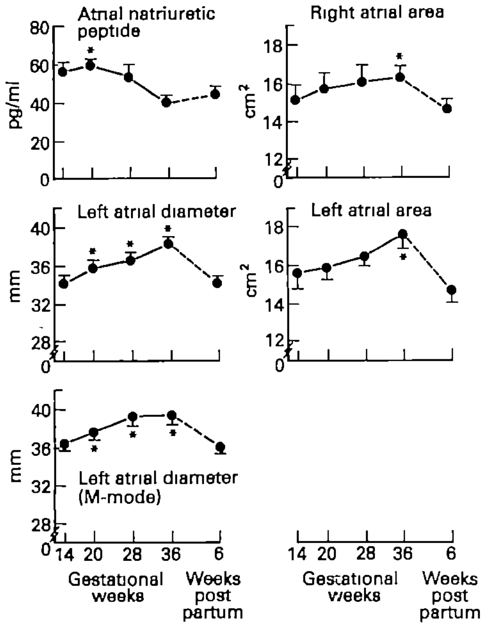

Fig. 1. Mean values of ANP, right atrial area, left atrial area and left atrial diameter during pregnancy and 6 weeks post partum. Bars represent the SE. Asterisks (*) indicate significant differences from values 6 weeks post partum.

tum. Mean values of the area of the right and left atrium and the left atrial diameter showed a gradual rise during gestation. Right and left atrial areas were significantly greater at 36 weeks than at 6 weeks after delivery. Left atrial diameter was already significantly increased by 20 weeks gestation and had increased further by 36 weeks.

Table 1 lists the ranges, pooled weighted means and the 95% CI of the individual coefficients of correlation of ANP with the atrial dimensions (all correlations appeared to be homogeneous). ANP was neither significantly correlated with right or left atrial areas nor with the diameter of the left atrium.

Discussion

In our study, plasma ANP concentrations were found to be significantly elevated during mid-pregnancy compared with 6 weeks post partum. ANP levels during the third trimester of pregnancy were not significantly different from those at 6 weeks post partum, which confirms some cross sectional studies (Doniec-Ulman *et al.* 1987, Grace *et al.* 1987, Elias *et al.* 1988, Shrivastav *et al.* 1988, Hirai *et al.* 1988, Stratta *et al.* 1988, Bond *et al.* 1989) as well a serial one by Fiévet *et al.* (1988). The results are also in agreement with our earlier study (Steegers *et al.* 1987) which showed that from 34 weeks gestation onwards ANP levels were not different from those at 6 weeks post partum. Serial measurements by Milsom *et al.* (1988) showed a continuous rise in concentrations of ANP in plasma, reaching maximal values in the third trimester which were significantly higher than at 6 weeks after delivery. Others who measured ANP levels serially throughout pregnancy did not find a change at all (Malatino *et al.* 1988).

In contrast to the pattern of change in ANP levels, right and left atrial areas and the diameter of the left atrium were all significantly increased in the third trimester of pregnancy. None of these atrial measurements appeared to be significantly correlated with plasma ANP concentrations whereas in the non-pregnant state left atrial diameter and ANP concentration in the central circulation have been reported to be positively correlated (Rodeheffer *et al.* 1986).

One explanation for the lack of correlation between plasma ANP and atrial size during pregnancy can be that the atrial dimensions were not measured correctly. However, two-dimensional echocardiographic determination of atrial size is known to be highly correlated with angiocardiographic measurements (Gonska *et al.* 1984). Besides, in our study the increase in the diameter of the left atrium was demonstrated by two different techniques of echocardiography. Furthermore, such a rise in left atrial diameter (as measured by M-mode echocardiography) has been reported previously by others (Katz *et al.* 1978, Robson *et al.* 1989).

Another explanation could be that atrial size

Table 1. Coefficients of correlations of ANP with atrial dimensions

	Range	Pooled mean	95% CI
Right atrial area	−0·92 to 0·85	−0·06	−0·61 to 0·53
Left atrial area	−0·62 to 0·80	0·24	−0·36 to 0·70
Left atrial diameter	−0·70 to 0·62	−0·09	−0·56 to 0·42
Left atrial diameter (M-mode)	−0·90 to 0·98	−0·07	−0·52 to 0·41

is an incomplete index for atrial stretching. The degree of atrial stretch is related not only to atrial dimensions but also depends on intracavitary atrial pressure and on atrial wall distensibility, but these measurements require invasive techniques. Right atrial pressure and pulmonary capillary wedge pressure during pregnancy have been reported to be within normal non-pregnant limits (Visser *et al.* 1987, Bader *et al.* 1955, Mashini *et al.* 1987), but no serial measurements have been made so far.

An absence of a rise in atrial pressure, despite the increase in circulating volume, could be due to the functional enlargement of the maternal vascular bed, together with a structural increase in cardiac dimensions due to cardiac hypertrophy as reported by Robson *et al.* (1987a).

A different explanation for ANP levels failing to be continuously elevated in association with long-term hypervolemia can be that atrial volume receptors are reset or have a decreased sensitivity during chronic atrial dilatation. In rat pregnancy it has been shown that despite an increased intravascular volume of 70%, cardiac content of ANP is similar to that in virgin rats (Kristensen *et al.* 1986), which might suggest that the regulation of ANP secretion during pregnancy takes place around a new volume 'set-point'.

During the first days after delivery the rise in intravascular volume, due to a shift of interstitial fluid into the circulation, and the subsequent increase in atrial size (Robson *et al.* 1987b) result in an increase in ANP levels (Rutherford *et al.* 1987, Steegers *et al.* 1987). In contrast to the pregnant state, atrial volume receptors seem to recognize that the intravascular volume is expanded. This again suggests that plasma ANP concentrations reflect an increase in circulating volume only in relation to the size of the vascular compartment, because after delivery there is reversal of the systemic vasodilatation accompanying pregnancy. It may also suggest that ANP levels reflect an increase in circulating volume only if such a rise takes place within a relatively short period of time.

In conclusion, our results show that plasma ANP concentrations during pregnancy are not related to atrial size. This might point to an altered mechanism of ANP secretion, which may be part of a purposeful physiological adaptive process to sustain the hypervolaemia of pregnancy.

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Induced abortions, contraceptive practices, and tobacco smoking as risk factors for ectopic pregnancy in Athens, Greece

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Summary. A case-control study of the role of induced abortion and other factors on the subsequent occurrence of ectopic pregnancy was undertaken in 1986–1987 in Athens, Greece, where a similar study 20 years ago found a tenfold risk of ectopic pregnancy among women with one or more illegal induced abortions. Seventy women residents of Athens, consecutively admitted to the major state maternity hospital with a diagnosis of ectopic pregnancy, were individually matched with women with a newly diagnosed pregnancy of the same order as the ectopic index pregnancy. Two control women were found for each of 63 cases, but only one control for each of the remaining seven cases. All cases and controls were interviewed by the same qualified obstetrician. Statistical analysis was undertaken with stratification of individual matched triplets and pairs, as well as through conditional multiple regression procedures. The relative risk of recurrence of an ectopic pregnancy was 6·39 with 95% confidence interval (CI) 1·96–21·04. Miscarriages did not increase the risk of ectopic pregnancy. The relative risk for subsequent ectopic pregnancy among women with one or more induced abortion, compared to women without such abortions, was 1·87 (CI 0·84–4·16) controlling only for the matching factors, and 1·71 (CI 0·69–4·27) when marital status (a possible selection factor) was also accounted for in the conditional logistic regression. There was no evidence for increasing risk with increasing number of induced abortions. Past use of an intrauterine device (IUCD) was associated with a relative risk of 3.89 (0·72–21·02); the relative risk increased with the duration of use of the IUCD. Tobacco smoking significantly increased the risk of an ectopic pregnancy, the relative risk being 2·35 (CI 1·19–4·67). Legalized induced abortions, as currently practised in Greece, do not appear to increase the relative risk of ectopic pregnancy to a substantial degree.

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Ectopic pregnancy occurs when the fertilized ovum is implanted outside the uterine corpus—usually in the fallopian tubes. In many developed countries it accounts for more than 10% of maternal deaths, and in the USA it represents the leading cause of maternal deaths during the first trimester of pregnancy (Atrash *et al.* 1986). Several factors have been examined in cohort; case-control, cross-sectional, ecologic and clinicopathologic studies; their results have been thoroughly and thoughtfully reviewed by Chow *et al* (1987). It appears that the *relative risk* of an ectopic pregnancy increases with the age of the woman, history of pelvic inflammatory disease, history of sexually transmitted diseases, use of intrauterine contraceptive devices (IUCD), tubal sterilization, history of infertility, and past pelvic (mainly tubal) operation, whereas use of oral contraceptives and miscarriages appear unrelated to ectopic pregnancy, and barrier contraceptive methods may actually reduce its occurrence (Chow *et al* 1987; Marchbanks *et al.* 1988; Makinen *et al.* 1987). However, the established risk factors do not account for most ectopic pregnancies and cannot explain the long-term incidence trends. A marked secular increase has been noted in many developed countries, including the USA, UK and Scandinavian countries, and most authors agree that this is, at least in part, real (Atrash *et al.* 1986; Makinen *et al.* 1987; Hemminki & Heinonen 1987; Thorburn *et al.* 1987; Flett *et al* 1988). A factor with potential aetiologic importance is induced abortion. Abortions can lead to pelvic inflammatory diseases (particularly when done under inadequate conditions) and their frequency has apparently increased in many countries of the world. Most analytic epidemiological studies (Chow *et al.* 1987; Makinen *et al.* 1987; Hogue *et al.* 1982; Holt *et al.* 1989) have found small increases of the relative risk of ectopic pregnancy among women with one and, particularly, more than one induced abortion, but a relative risk of 10·4 was reported from Greece at a time when induced abortions were illegal (Panayotou *et al.* 1972). However, Weiss *et al.* (1985) have pointed out that case-control studies using as controls women *completing* full-term pregnancies (Panayotou *et al* 1972; Levin *et al.* 1982; Daling *et al.* 1985) may overestimate the relative risk associated with induced abortion, because women willing to allow a pregnancy to proceed are likely to have a lower than average frequency of induced abortions in their reproductive histories. To address these issues, a case-control study was undertaken in Greece in the same geographical and institutional setting as the previous one (Panayotou *et al.* 1972) Now (1986–1987), 20 years after the earlier study (data of Panayotou *et al.* 1972 were collected in the late sixties), induced abortion has been legalized in Greece and socio-economic and medical conditions have substantially improved. Furthermore, the study design was modified to accommodate the observation of Weiss *et al.* (1985) that a bias is likely when control women are completing full-term pregnancies (rather than being simply diagnosed as pregnant, without prejudice as to potential outcome).

Subjects and methods

During a 18-month period between 1986 and 1987, 70 women residents of Athens with diagnosis of ectopic pregnancy (cases) were admitted to the Alexandra teaching hospital, the major of two state maternity hospitals in the Athens area (also served by five private maternity hospitals). During the same period, about 3500 women visited the outpatient clinics of the same maternity hospital at an early stage of their pregnancy or were diagnosed as pregnant in these clinics (many of these women had their pregnancies terminated or were delivered subsequently in one of the private maternity hospitals in Athens). For every case two control women were sought among the outpatients: they had to be residents of Athens; to be of about the same age (±3 years) and of the same educational status (±2 schooling years—years of schooling have been repeatedly found (Trichopoulos 1982) to represent the best socio-economic indicator in Greece); and to be at the same early stage of a pregnancy (exact matching) as the ectopic pregnancy of the case (index pregnancy). Three of the control women had had an ectopic pregnancy before the index pregnancy and they were considered separately. Two control women, matching for residence, hospital, approximate date of interview, age, socio-economic status and parity were found for each of 63 cases, whereas only one control woman was found for each of the remaining seven cases.

Cases and controls were interviewed in person by one of us (M.D.). Because the interviewer was an obstetrician and a member of the medical staff of the hospital there were no refusals. Questionnaires covered demographic, socio-economic and medical data, as well as reproductive histories and contraceptive practices.

Reproductive history data were analyzed with

Table 1. Demographic and biometric characteristics of 70 women with ectopic pregnancy and 133 control women (63 triplets and 7 pairs, matched for age, years of schooling and parity)

Characteristic	Cases (%)	Controls (%)
Age (years)		
–19	7·1	3·8
20–24	30·0	28·6
25–29	24 3	30·8
30–34	25·7	20·3
35+	12·9	16·5
Years of schooling		
0	2·9	3·0
1–5	2·9	1·5
6–11	55·6	54·9
12+	38·6	40·6
Occupation		
Manual	12·9	9 8
Non-manual	38·6	23·3
Housewife	48·5	66·9
Height (cm)		
Mean (SE)	163·3 (0·8)	162·0 (0·6)
Weight (kg)		
Mean (SE)	61 7 (1·1)	60·4 (0·9)
Age at menarche (years)		
−12	35·7	39·8
13	35·7	27·9
14	21·4	18·0
15+	7·2	14·3
Menstrual regularity		
Regular	85·7	87·2
Irregular	14·3	12·8
Marital status		
Single and separated	37·1	3·1
Married	62·9	96·9
Tobacco smoking		
Never	35·7	61 7
Past	4·3	4·5
Present	60·0	33·8

Results are percentage or mean (SE) values as appropriate.

stratification of the individual matched triplets and pairs (Rothman & Boice 1979, Miettinen 1985) (this procedure does not permit control of confounding by variables other than those used in the individual matching) and by conditional logistic regression (Breslow & Day 1980; Schlesselman 1982) (this procedure is conceptually and technically more complicated but allows control of additional confounding variables).

Results

In Table 1 demographic and biometric characteristics of cases and controls are shown. The two groups were similar with respect to age and years of schooling (matching variables) and fairly similar with respect to occupation (there is little, if any, overall socio-economic differentiation between women working in non-manual occupations and those identifying themselves as housewives in Greece), menstrual history and somatometric variables. By contrast, cases and controls were very different with respect to marital status and smoking habits, cases being more likely to be single (or separated) and current smokers. Consequently, these two variables were included in the conditional multiple logistic regression analysis.

Table 2 summarizes the reported patterns of contraceptive practices by women in the two groups. No woman in either group reported surgical sterilization or use of a diaphragm, and few women, equally distributed among cases and con-

Table 2. Contraceptive practices by 70 women with ectopic pregnancy and 133 matched control women

Contraceptive practice	Cases (%)	Controls (%)
Oral contraceptives		
Never	85·7	91·7
Ever	14·3	8·3
Diaphgram		
Never	100·0	100·0
Ever	0·0	0·0
Vaginal creams and suppositories		
Never	98 6	99·2
Ever	1·4	0·8
Coitus interruptus		
Rarely	62·8	39·8
Frequently	37·2	60·2
Condom		
Rarely	65·7	82·7
Frequently	34·3	17 3
Rhythm		
Rarely	87·1	88·0
Frequently	12·9	12·0
Surgical sterilization		
No	100·0	100·0
Yes	0·0	0·0
Intrauterine device (years of use)		
Never	90·0	97·6
≤2	5·7	1·6
≥3	4·3	0·8
Any contraceptive		
Never or rarely	20·0	9·0
Frequent	80·0	91·0

trols, reported use of vaginal preparations or application of the rhythm method. Coitus interruptus was reported more frequently by controls and condom use more frequently by cases, but both associations were substantially reduced in the conditional analyses, are not supported in the literature, and are not biologically plausible. They were not further explored.

Both oral contraceptives (OC) and IUCDs were more frequently utilized by cases than by controls. The association with oral contraceptives was weak, could be easily explained by chance and almost disappears in the conditional analyses. By contrast, the overall association with use of IUCDs was stronger, biologically and bibliographically plausible, and significant ($P<0·05$) in nominal terms; therefore it was retained for investigation in the conditional analyses.

The present study was principally designed to assess the effect, if any, of previous reproductive outcomes, and, in particular, induced abortion on the subsequent occurrence of ectopic pregnancy. Among the 70 cases with an ectopic index pregnancy, eight had had one previous ectopic pregnancy and one had had two; among the 133 controls, three had had a previous ectopic pregnancy. The association was statistically significant and the estimated relative risk of recurrence of an ectopic pregnancy, given a previous one, was 6·39 with 95% confidence interval (CI) 1·94–21·04.

In the subsequent analyses the three controls with a history of an ectopic pregnancy were replaced with three different women without such a history, because some researchers claim (with arguable justification) that controls should not have had the condition under study. The difference, if any, in the present instance is clearly negligible.

Table 3 shows the outcomes of pregnancies preceding the index pregnancies in cases and controls. There was an indication that cases report more induced abortions and slightly fewer miscarriages than controls. The negative association between miscarriage and risk of ectopic pregnancy is not biologically plausible and can easily be explained by chance ($P>0·20$). By contrast, the positive association between induced abortion and ectopic pregnancy, assessed through procedures allowing the preservation of the matched sampling (Rothman & Boice 1979; Miettinen 1985), appeared stronger, although it did not reach statistical significance ($P = 0·10$); the estimated relative risk was 1·87 with 95% CI 0·84–4·16. Stratification by parity, without preservation of matching by age and years of schooling, in order to assess whether 'dose-response' existed with increasing number of induced abortions revealed no such pattern; the relative risk was almost identical whether one or more than one induced abortions preceded the index pregnancy.

Table 4 shows adjusted relative risks for an ectopic pregnancy in association with exposure (*vs* non-exposure) to particular factors for which there is either suggestive evidence for a casual role both in the relevant literature and in the present data (IUCD use, smoking, induced abortion), or strong evidence in the present data that they represent selection factors or genuine risk indicators (marital status). These relative risk estimates are derived from multiple conditional regression models that take into account the individual matching by age, years of schooling and parity Both marital status and tobacco smoking appeared to be, at least in this study, independent risk factors for ectopic pregnancy. Ever users of

Table 3. Outcome of pregnancies preceding the index pregnancy (current ectopic in 70 cases, same order marker pregnancy of unknown outcome in 133 matched controls)

	Cases		Controls	
Pregnancy outcome	Total	Mean	Total	Mean
Livebirth	56	0·80	129	0·97
Stillbirth	2	0·03	4	0·03
Miscarriage	15	0·21	40	0·30
Induced abortion	48	0·69	66	0·50
Previous ectopic pregnancy	10	0·14	0*	0·00
All outcomes	131	1·87	239	1·80†

* Three control women with previous ectopic pregnancy were excluded and replaced with three other matched control women.

† The difference in mean total previous pregnancies (1·87–1·80 = 0·07) corresponds to 9 previous pregnancies and is accounted for by the fact that for 7 high parity cases only one, rather than two, matched controls were found

IUCDs appeared also to be at excess risk for ectopic pregnancy, although the association was not statistically significant, possibly because IUCD users were very few in this study. The positive association with induced abortion, already modest (relative risk 1·87), and non significant when only the matching factors were accounted for in the analysis (Model 1), was further reduced when marital status, use of IUCD and, particularly, tobacco smoking were introduced into the model.

The association between IUCD use and the risk of ectopic pregnancy was further examined by taking duration of use into account. Among long-term users, i.e., those who had used IUCDs for >2 years, the relative risk was 6·19, with a one-tail exact test approaching nominal significance (Miettinen 1985). By contrast, the relative risk among short-term users was lower and its difference from the null value of 1 can be attributed to chance.

Discussion

The present study is a typical hospital-based matched case-control study and has all the associated strengths and limitations. It is inherently more powerful than a cohort study addressing the same problem, because induced abortion is relatively common and ectopic pregnancy relatively rare; exact matching for parity further increases the power, since the cumulative probability of both an ectopic pregnancy and at least one previous induced abortion increases with the number of pregnancies, making it necessary to control for birth order; and patient cooperation is high, minimizing refusal rates and improving the quality of information. On the other hand, comparability between cases and controls may not be optimal, because selection factors may operate with different forces for cases and controls. Thus, cases with ectopic pregnancy are more likely to be admitted to a major teaching hospital, whereas both abortions and normal deliveries may be undertaken in any of the private maternity hospitals in the area. Both marital status and socio-economic level may be related with these differential selection forces and may be responsible for the observed difference between cases and controls by marital status in this series. Nevertheless, matching by years of schooling and controlling for marital status in the conditional logistic regression analysis would be expected to reduce substantially, if not to eliminate completely, any associated bias.

Table 4. Adjusted relative risks for ectopic pregnancy (and 95% confidence intervals) associated with exposure to the indicated factors Multiple conditional logistic regression derived estimates, controlling through matching for age (±3 years) years of schooling (±12 years) and parity (exactly)

Variable	Model 1	Model 2	Model 3	Model 4
Currently married (*vs* not)		0·06 (0·02–0·27)	0·08 (0·02–0·35)	0·07 (0·02– 0·32)
Ever users of IUCD (*vs* never)				3·89 (0·72–21·02)
Smokers (*vs* non-smokers)			2·45 (1·25–4·83)	2·35 (1·19– 4·67)
Any induced abortion (*vs* none)	1·87 (0·83–4·20)	1·71 (0·69–4·27)	1·52 (0·59–3·93)	1·32 (0·49– 3·57)

With respect to induced abortions the results of the present study are markedly different from those of the earlier Greek study (Panayotou *et al* 1972), although the confidence intervals of the two relative risk estimates overlap (in the earlier study the relative risk was 10·4 with 95% CI 2·8–37·8, whereas in the present one the relative risk is 1·71 with 95% CI 0·69–4·27). There are four possible reasons which may explain this difference: chance, mainly in the earlier and smaller study, since the lower confidence limit in that study was only 2·8; an element of bias, also in the earlier study, because of inappropriate control definition, as pointed out by Weiss *et al.* (1985); gradual substitution, in the maternity hospitals of Athens, since the late sixties, of the probably safer suction procedure in place of dilatation and curettage as the standard technique for induced abortions; and gradual liberalization, during the last 30 years, of the attitudes of Greek society as far as abortions are concerned—a liberalization that was probably accompanied by improvements in the conditions under which the operations were undertaken (under certain provisions, which can be easily fulfilled or bypassed, abortions are now legal in Greece).

The collective evidence concerning the link between induced abortion as currently practised in developed countries, and the risk of a subsequent ectopic pregnancy indicates that if an association exists it is weak, of small public health significance and of negligible importance to individual patients. Among the nine studies reviewed and tabulated by either Hogue *et al.* (1982) or Chow *et al.* (1987) and three published subsequently (Marchbanks *et al.* 1988; Makinen *et al.* 1987; Holt *et al.* 1989), nine found an increased risk, whereas in the remaining three the relative risk was less or equal to 1·0. If the selection bias pointed out by Weiss *et al.* (1985) is accounted for (this bias may by itself generate a relative risk of 1·5), the corrected average relative risk for an ectopic pregnancy following one or more induced abortion would appear to be around 1·5, and possibly lower in the USA and other highly developed countries or population groups. A relative risk of this order is compatible with the occasional complication of some induced abortions by pelvic inflammatory disease, and the moderately strong association believed to exist between pelvic inflammatory disease and ectopic pregnancy (Levin *et al.* 1982; World Health Organization 1985).

Intrauterine devices are thought to exercise their effect, at least partly, by producing a sterile inflammatory condition hostile for ovum implantation (Moyer & Mishell 1971). In some case-control studies (reviewed and tabulated by Chow *et al.* 1987 and Coupet 1989), an elevated risk of ectopic pregnancy has been associated with past use of an IUCD, and a further association with duration of past use was noted. The results of the present investigation are compatible with these observations, but the limited utilization of IUCDs in the Greek population did not allow firm statistical substantiation of the findings. The collective empirical evidence and the presumed causal link between IUCD use and pelvic inflammatory disease (Westrom *et al.* 1976) make the causal association between past use of an IUCD and ectopic pregnancy epidemiologically and biologically plausible. Since, however, current use of an IUCD reduces the absolute occurrence of ectopic pregnancies (even though it may increase their relative frequency among current IUCD users by preventing more effectively intrauterine than extrauterine pregnancies) it is unlikely that the observed secular increase of the incidence of ectopic pregnancies in several developed countries could be explained in terms of more frequent use of IUCDs by the respective populations.

The results of the present study are also compatible with earlier well substantiated findings indicating that ectopic pregnancies have a strong tendency to recur (Levin *et al.* 1982; World Health Organization 1985) and that prior use of oral contraception does not substantially affect the relative risk of subsequent ectopic pregnancies (studies reviewed by Chow *et al.* 1987).

An unexpected finding, but one which has already been reported in at least three other studies (Levin *et al.* 1982; World Health Organization 1985; Matsunaga & Shiota 1980), was the fairly strong and statistically significant association between tobacco smoking and ectopic pregnancy. This association, if real and causal, could be mediated through one or more of the many established or postulated pathophysiological effects of tobacco smoking, including those on the immune system (Hersey *et al.* 1983) and the production rates of oestrogens (MacMahon *et al.* 1982).

In conclusion, among the factors investigated in the present and in earlier studies, none appears to account for a substantial fraction of ectopic pregnancies or to explain the observed secular increase of their occurrence. If the relative risks associated with induced abortion and tobacco smoking reflect causal relations and are indeed around 1·5 and 2·0, respectively, as the collective evidence seems to indicate, these factors should be further explored since their high frequency in many populations could generate high attributable risks even if the corresponding relative risks are modest. Simultaneously or alternatively, more emphasis should be given to the possible causal role of pelvic inflammatory and sexually transmitted diseases, particularly those attributed to *Chlamydia trachomatis* infections, since their incidence seems to be high and rising, and the evidence concerning their contribution to the aetiology of ectopic pregnancy appears rather strong.

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The vanishing bowel. Case report of bowel atresia following gastroschisis

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Case report

A 20-year-old woman booked at 17 weeks gestation for antenatal care in her third pregnancy. There was no family history of congenital disease and she was teetotal, a non-smoker and had not been exposed to drugs during the pregnancy. A routine ultrasound examination at 17 weeks revealed many loops of bowel floating free in amniotic fluid. The bowel was outside the fetal abdominal cavity to the left of the umbilical cord insertion. A diagnosis of gastroschisis was made and this was confirmed 4 weeks later by a second ultrasound scan (Fig. 1). No other abnormality was noted. She was advised about the diagnosis and the good prognosis was explained. The remainder of the pregnancy was uneventful. She had no further scans and at 38 weeks gestation she reported to the labour ward. After a 20-h labour augmented with oxytocin and an amniotomy which revealed clear amniotic fluid, she gave birth to a 3·3 kg male fetus in good condition. The placenta and cord were completely normal. To his surprise the attending paediatrician could find no phenotypical abnormalities. The abdominal wall was intact. The baby was returned to the mother who commenced breast feeding. The baby showed little interest in food and 9 h later vomited green bile. An abdominal X-ray revealed a distended stomach and no gas in the mid or hind gut. A radiological diagnosis of high intestinal obstruction was followed by laparotomy where agenesis of the baby's entire small bowel was found, along with a dilated blind ending duodenum and a microcolon. There was clearly insufficient bowel for survival and to prevent the infant from dying from an intestinal obstruction a high duodenostomy was performed. As no corrective surgical procedure was possible, and after discussion, it was felt pointless to persist with what would have been a lifetime of intravenous feeding. The baby was made comfortable and he spent most of the weekend at home with his parents where he died peacefully during the night, 4 days after his birth.

Discussion

Gastroschisis and eventration are terms applied to extensive absence of abdominal wall. No sac is present and the umbilical cord is attached to one side of the defect, usually the left. The ultrasonographic features are characteristic and our patient had all the classical features

In view of the antenatal diagnosis of gastroschisis it is interesting to speculate that this patient may have represented an in-utero midgut evisceration which underwent an early volvulus followed by bowel ischaemia and necrosis with subsequent resorption and then closure of the abdominal wall defect. Babies with gastroschisis can develop prenatal bowel ischaemia and necrosis attributable to volvulus, torsion and narrowing of the abdominal wall opening (Reinberg 1989). Although localized bowel stenosis and atresia is associated with gastroschisis (Bair *et al.* 1986; Moore 1977) these lesions may be coincidental. However, it is known that in utero ligation of the mesenteric artery in fetal puppies leads to intestinal infarction, reabsorption and atresia (Louw 1966) and the disappearance of bowel in our case suggests that the gastroschisis caused ischaemia and subsequent atresia. It is

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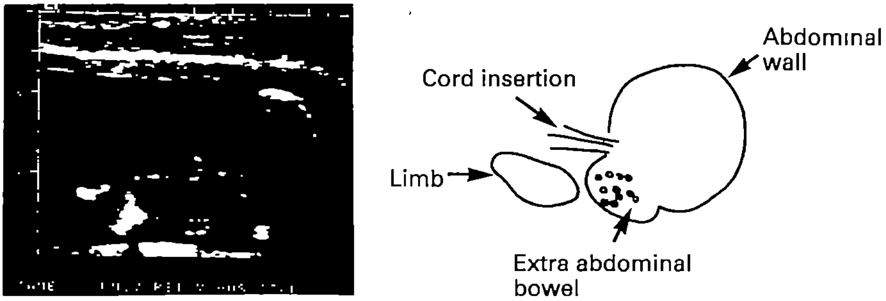

Fig. 1. An ultrasonogram at 20 weeks gestation showing the abdominal wall defect to the right of the cord insertion

known that wounds inflicted on the second trimester fetus resolve without scarring and therefore the absence of an abdominal wall lesion in this infant suggests that the vascular accident occurred late in the second trimester.

Congenital intestinal atresia is thought to occur because of an intrinsic developmental abnormality in the gut or a vascular accident in fetal life. This case adds support to the view that intestinal atresia can occur due to vascular accidents in the second trimester.

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Renal failure in pregnancy due to primary renal lymphoma. Case report

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Case report

A 29-year-old woman at 32 weeks gestation was admitted with a small antepartum haemorrhage after a previously uneventful pregnancy. Malaise for 3 weeks was her only other symptom. Her blood pressure was 150/90 mmHg. There were no signs of placental abruption. No fresh vaginal bleeding was seen. She had proteinuria (3+), but the urinary deposit was normal on microscopic examination. Ultrasound confirmed a normally situated placenta without evidence of separation. The pattern of the fetal heart rate was normal.

She was anaemic (haemoglobin 8·1 g/dl compared with 12·5 g/dl in early pregnancy) but her white cell and platelet counts were normal. She was in renal failure: urate 752 mmol/l, creatinine 603 mmol/l, urea 30·6 mmol/l, sodium 135 mmol/l and potassium 4·7 mmol/l, although the urinary output was normal.

That evening the fetal condition deteriorated and she was delivered by emergency caesarean section. A male infant weighing 1430 g was born with Apgar scores of 9 and 10 at 1 and 5 min respectively, umbilical artery blood pH 7·28 and base deficit of 11·5 mmol/l.

Post-operatively, her urinary output remained between 1600–1800 ml 24 h. The blood pressure settled to 130/90 mmHg without treatment. Transient hyperkalaemia was treated with calcium resonium. The urate, urea and creatinine remained high at 776/mmol/l, 32·6 mmol/l and 725 mmol/l respectively. The 24-h urinary protein was 1·0 g. Total serum proteins were 72 g/l, with 33 g/l albumen. Serum calcium was 1·75 mmol/l and phosphate 2·3 mmol/l. Renal ultrasound showed bilaterally enlarged, non-homogenous, hypoechoic kidneys (13 cm and 14 cm) with irregular outlines. There was no calyceal obstruction (Fig. 1).

There was no evidence of immunological disease (antinuclear antibody, antineutrophil cytoplasmic antibody and antiglomerular basement membrane antibody titres all negative; IgG 9·9 mg/ml, IgA 4·8 mg/ml, IgM 1·43 mg/ml, C3 111 mg/dl, C4 32·5 mg/dl), although the C-reactive protein was elevated at 17·4 mg/dl.

A left renal biopsy revealed severe damage. Glomerular capillary obliteration, total tubular atrophy and marked interstitial fibrosis were present. Infiltration by a high grade, B cell non-Hodgkin's lymphoma (Fig. 2) was confirmed by marker studies.

She did not have overt lymphadenopathy or hepatosplenomegaly and there was no evidence of extra-renal lymphoma in the bone marrow or cerebrospinal fluid, nor on examination of the chest and abdomen by tomography.

The patient developed nausea, vomiting and anorexia. She was treated with intermittent haemodialysis. Chemotherapy was started with prednisolone, vincristine, adriamycin and intrathecal methotrexate Subsequently, she was treated according to the MACOP-B protocol (Klimo & Connors 1985).

Renal function improved rapidly; within 10 days she was independent of dialysis with a creatinine clearance of 14 ml/min. The last plasma creatinine concentration was 235 mmol/l.

Ultrasound showed that the kidneys have returned to normal size with a pattern of increased echogenicity. A right renal biopsy taken 11 weeks after chemotherapy started showed renal damage as before but no residual tumour. Repeat computed tomography showed no evidence of lymphoma at distal sites. This suggests that remission has been achieved.

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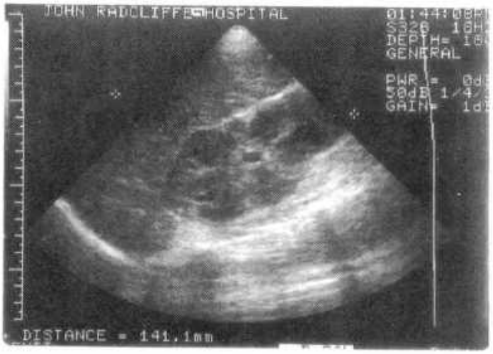

Fig. 1 Ultrasound scan of right non-homogenous hypoechoic kidney showing irregular outline. (Courtesy of Dr D. Linsell.)

Comment

Renal failure secondary to lymphomatous infiltration of the kidneys is rare and generally occurs in patients with extrarenal disease (Richmond *et al.* 1962). The diagnosis requires biopsy evidence of lymphoma and the demonstration of prompt improvement in renal function with treatment. Our patient had a primary renal lymphoma presenting with renal failure in pregnancy. To our knowledge this has not been described before.

The differential diagnosis of renal failure in a patient presenting with an antepartum haemorrhage must include placental abruption but the haemodynamic stability, urinary output and biochemistry of our patient were consistent with a less acute process.

The ultrasound observation of bilaterally enlarged, non-homogenous kidneys further limited the likely causes of renal failure which would include acute glomerulonephritis, diabetic nephropathy, amyloidosis or lymphomatous infiltration. This bilateral enlargement and the absence of extrarenal manifestations of disease made diagnosis by renal biopsy essential.

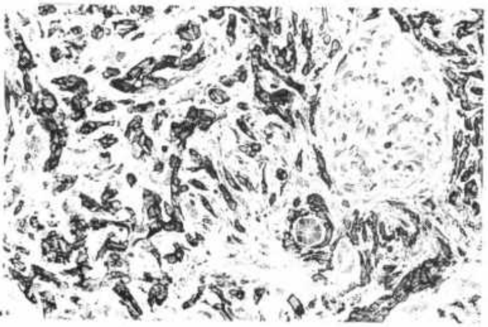

Fig. 2 Renal biopsy stained immunocytochemically to demonstrate immunoglobulin on infiltrating cells. (Courtesy of Dr M. S. Dunnill).

Lymphomatous infiltration of the kidneys has been shown to respond promptly to treatment and so early diagnosis is important (Glicklich *et al.* 1986). The rapid response to specific chemotherapy in our patient confirms that the lymphoma was implicated in the renal failure.

The mechanism of renal failure in diffuse infiltration is unclear, intrarenal obstruction being one possibility (Suki 1981).

The first line treatment of stage 1 lymphoma is usually radiotherapy or surgery but chemotherapy was the preferred treatment because radiotherapy or surgery would have further reduced renal function and necessitated renal replacement therapy. Also, while the radiological and histological features described here are consistent with primary renal lymphoma (Truong *et al.* 1987), chemotherapy was chosen because of the possibility of undetected extrarenal lymphoma. The subsequent course and investigations in this patient suggest, however, that this was a truly primary renal lymphoma.

Acknowledgments

We would like to thank Dr C. Winnearls, Dr D. Oliver and Dr C. Bunch for allowing us to report their patient. We are also grateful to Dr D. Linsell and Dr M. Dunnill for their help with the ultrasonography and histology respectively.

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Increased platelet turnover in a patient with previous recurrent pre-eclampsia and failure of aspirin therapy. Case report

Y. AHMED, M. H. F. SULLIVAN, M. G. ELDER

Case report

The patient was a 36-year-old Caucasian who had had two pregnancies complicated by gestational hypertension and two with pre-eclampsia (as defined by Davey & MacGillivray 1988) with no resulting live births (see Table 1). The outcome of a fifth pregnancy was a blighted ovum. All pregnancies were with the same partner. Between pregnancies she appeared healthy and was normotensive. The features of each pregnancy, including the complications, treatments and maternal and fetal outcomes are summarised in Table 1. Investigations have excluded phaeochromocytoma, systemic lupus erythematosus and renal disease. A pelvic angiogram excluded an abnormality of uterine vessels that might lead to reduced placental blood flow. During her last pregnancy our patient was treated with 75 mg of aspirin daily from 12 weeks onwards, but this did not prevent pre-eclampsia. After this last pregnancy, platelet lifespan and platelet aggregometry were estimated to assess in-vitro platelet function in order to investigate the apparent lack of benefit from aspirin.

Platelet lifespan was assessed by a nonradioisotopic method as described by Patrignani *et al.* (1982), that involves measuring the serum concentration of thromboxane B_2 (TXB_2). This compound is the stable metabolite of thromboxane A_2 (TXA_2), and is produced maximally by platelets during clotting. Aspirin irreversibly acetylates the platelet cyclo-oxygenase enzyme and this prevents thromboxane production. Therefore, serial serum measurements of TXB_2 after oral ingestion of 300 mg asprin reflect thromboxane production by new platelets that have not been exposed to aspirin in the circulation. The recovery of TXB_2 levels to those preceding aspirin treatment is a measure of platelet production *in-vivo*. In our patient serum thromboxane returned to pre-treatment levels within 3·3 days compared with 8 days in a control subject; this is similar to the normal platelet lifespan reported elsewhere as 8–11 days (Stuart *et al.* 1975; Wallenburg & van Kessel 1978). Platelet numbers in both the above subjects were unaffected by 300 mg aspirin. In-vitro platelet aggregation was assessed using the turbimetric method described by Born (1962). Platelets were stimulated using the aggregating agent ‘platelet activating factor’ (PAF). Platelets from our patient required only 1 nM PAF to stimulate maximal aggregation compared with 10–20 nM PAF which was required to aggregate platelets from normotensive non-pregnant controls.

Discussion

Pre-eclampsia is a disease of pregnancy which occurs primarily in the first pregnancy of a particular partnership (MacGillivray 1958), but a minority of women continue to have this disorder in a series of pregnancies (Campbell & MacGilivray 1985). An imbalance in the ratio of TXA_2, a potent vasoconstrictor and platelet aggregatory agent, to prostacyclin (PGI_2) a vasodilator and platelet anti-aggregatory agent, in favour of TXA_2 may account for the decreased uteroplacental blood flow and maternal hypertension present in pre-eclampsia (Walsh 1985). Platelets are a major source of TXA_2, the production of which can be inhibited selectively by low-dose aspirin which irreversibly acetylates the platelet cyclo-oxygenase enzyme (Patrignani *et al.* 1982). This property of

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Table 1. Previous obstetric history

Age (years)	Complications	Treatment	Result	Postnatal
24	Gestational hypertension BP 150/110*	Nil	IUD at 27 weeks, fetal weight 500 g, placental weight 200 g	BP 130/80 at 2 weeks postnatal
25.	Gestational hypertension BP 190/130* at 25 weeks, acute renal failure	Methyl dopa sub-cut heparin from 23 wks	Termination of pregnancy at 25 weeks, weights unavailable	BP 110/70 at 6 weeks postnatal
26	Pre-eclampsia BP 140/90* 2 3 g/l proteinuria	Methyl dopa PG12 infusions at 24 wks	IUD at 25 weeks fetal weight 450 g (female) placenta 100 g	BP 125/75
31	Normotensive (BP 125/75)	blighted ovum at 10 weeks.	Evacuation of retained products.	
32	Pre-eclampsia BP 185/110* 2+ proteinuria	Methyl dopa, aspirin (75 mg daily)	IUD at 24 weeks fetal weight 276 g placenta not known	BP 120/80

*Maximum blood pressure (BP) in mm Hg.
IUD = intrauterine death.

low-dose aspirin has been the rationale for its use as a therapy to decrease the occurrence of pre-eclampsia in at-risk women although this may not be always successful (Beaufils *et al.* 1985; Wallenburg *et al.* 1986; Elder *et al.* 1988), as was the case in our patient.

Platelet lifespan is slightly decreased in normal pregnancy (Wallenburg & van Kessel 1978) and significantly decreased in pre-eclampsia (Rakoczi *et al.* 1979). Even when not pregnant our patient had a very short platelet lifespan and this may have been even shorter during her pregnancies. In individuals with normal platelet lifespan one low-dose aspirin tablet (75 mg) eliminated 50% of platelet function within 24 h and 90% inhibition was achieved after the administration of a second low-dose aspirin tablet (Sullivan *et al.* 1990). Assuming a platelet lifespan of 3·3 days during pregnancy in our patient, there would be only 20% inhibition of platelet thromboxane production 24 h after the initial aspirin, 30% after 48 h, and no more than a maximum of 35–40% inhibition despite daily aspirin administration. It would seem that our patient might benefit from additional suppression of platelet aggregation if any further attempts at pregnancy were to be made. Thromboxane synthetase inhibitors (e.g., Dazoxiben) (Van Assche & Spitz, 1988) or calcium channel blockers (e.g., nifedipine) (Lindow *et al.* 1988) have been used with beneficial effects in patients with third trimester pre-eclampsia. Both these compounds would be expected to inhibit platelelt aggregation (Han *et al.* 1983; Heptinstall *et al.* 1980), but so far they have not been used from early pregnancy for the prevention of pre-eclampsia.

The cause of the very short platelet lifespan in our patient would seem to be extreme hypersensitivity to aggregatory stimuli, as typified by the in-vitro PAF response, but the reason for this hypersensitivity is still unknown.

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Hypothyroidism presenting as hypothermia following pre-eclampsia at 23 weeks gestation. Case report and review of the literature

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Case report

A 21-year-old primigravida was admitted to hospital at 23 weeks gestation with a 3-week history of progressive oedema of her legs and face. Blood pressure (BP) recordings ranged from 130/80 to 140/100 mmHg and 4+ proteinuria was noted. Three days later she was transferred to the Women's College Hospital. She had mild dysphagia but no other complaints. She had been treated for anaemia in the past but denied any other medical problems; only later did she recall that she had had a goitre in the past. Her BP was 136/92 mmHg, pulse 82/min and her temperature was 36·8°C. Marked facial and peripheral oedema was noted. The thyroid gland was not palpable. Chest, cardiovascular and abdominal examinations were normal; the symphysis-fundal height was 20 cm. Reflexes were normal. Her voice was noted to be hoarse and her speech unclear, but the significance of these observations was not appreciated. Urine testing revealed 4+ proteinuria with normal microscopy and negative bacterial culture The haemoglobin level was 8·5 g/dl with normal red cell indices (mean corpuscular volume 95 fl) and film examination. The platelet count was 177 × 10^9/l and the coagulation profile was normal. Serum electrolytes, urea and creatinine concentrations were also normal, serum uric acid was in the upper range of normal at 340 mmol/l. Liver function tests showed mild elevation of aspartate transaminase at 50 U/l (normal 1–30 U/l) and lactate dehydrogenase at 264 U/l (normal 109–193 U/l), but normal alanine transaminase and bilirubin levels; serum total protein was reduced to 43 g/l (normal 60–80 g/l) and albumin was reduced to 21 g/l (normal 35–50 g/l) A 24-h urine collection contained 8·2 g protein and the creatinine clearance was 118 ml/min (normal range 84–132 ml/min) Serum iron and ferritin levels were normal. Antinuclear antibodies were absent. Ultrasound scanning showed an apparently normal 23 weeks gestation fetus with an estimated weight of 560 g.

A diagnosis of pre-eclampsia was made Methyldopa, 500 mg three times daily, was given orally On the third day after admission her BP rose to 150/105 mmHg and she was treated with a bolus dose of hydralazine 5 mg, intravenously. Later that day she complained to abdominal discomfort, her reflexes became more brisk and the serum fibrinogen degradation products (FDP) level was mildly elevated at 40 units; other laboratory tests were unchanged. The severity of pre-eclampsia was judged to be worsening and termination of the pregnancy was advised. Magnesium sulphate therapy was started. Labour was induced with an intravenous oxytocin infusion after a Foley catheter had been inserted into her long closed cervix to facilitate dilatation. The anaemia was corrected with a transfusion of 2 units of packed red cells. Because of the early gestational age, the fetal heart rate was not monitored. Sixteen hours later an immature male infant, weighing 563 g, was born The Apgar score was 1 both at 1 and 5 min after birth, and the infant was not resuscitated

Her BP remained stable at 110–120/80 mmHg

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during labour, delivery, and the postpartum period. By the following morning, there had been a diuresis of 3 litres and there was only a trace of proteinuria. Magnesium sulphate therapy was discontinued. Facial oedema and dysphagia improved but persisted. At 24 h postpartum her oral temperature was 33·5°C (it had once been recorded at 35·1°C on the day of delivery). Otherwise her vital signs, physical examination and routine laboratory investigations were unremarkable. A chest x-ray suggested a small left pleural effusion.

A tentative diagnosis of severe hypothyroidism was made. The patient was admitted to the intensive care unit and she was treated with a warming blanket and thyroid hormone replacement. Steroid therapy was added due to the possibility of complete pituitary failure. Her body temperature returned to normal overnight. Thyroid function tests confirmed severe hypothyroidism with a serum thyrotrophin (TSH) level of 96 mU/l (normal <5·5 mU/l), tri-iodothyronine (T3) level of 0·9 nmol/l (normal 1·2–3·4 nmol/l), thyroxine (T4) level of 15 nmol/l (normal 64–167 nmol/l) and T3 resin uptake of 0·27 (normal 0·35–0·45). Serum cortisol was 500 nmol/l. A triple bolus test, performed later, excluded hypopituitarism with the basal TSH of 220 mU/l increasing to >320 mU/L at 30 min after injection of thyrotropin releasing hormone. Her subsequent recovery, with maintenance thyroxine replacement therapy, was unremarkable.

Discussion

This patient presented at 23 weeks gestation with severe pre-eclampsia. Myxoedema was not suspected until hypothermia developed on the first day postpartum. In retrospect, her marked facial oedema, hoarse voice and dysphagia might have raised suspicion of myxoedema earlier. The extremely elevated TSH concentration was unlikely to have been related to pre-eclampsia, and suggests that the onset of hypothyroidism was not recent. It appears that pre-eclampsia masked the features of hypothyroidism in this patient.

Pregnancy in hypothyroid women is uncommon, due to frequent ovulatory dysfunction. When hypothyroidism is diagnosed in pregnancy there is an increased risk of miscarriage, stillbirth, preterm birth, congenital anomalies and developmental abnormalities (Greenman *et al.* 1962, Jones & Man 1969). Greenman *et al.* (1962) reported that only one of seven hypothyroid pregnant women gave birth to a normal, full term infant. Jones & Man (1969) found that 19·6% of hypothyroid pregnant women failed to give birth to a full term surviving infant compared with 12·6% of 1252 euthyroid women ($P<0·025$). Montoro *et al.* (1981) found a more favourable outcome with 9 of 11 pregnancies in nine hypothyroid women producing normal, full term infants. Although gestational age at diagnosis and duration of treatment before delivery varied greatly in these studies, clinical hypothyroidism appears to have an adverse effect on pregnancy outcome, overall.

In addition to increased perinatal morbidity and mortality, Davies *et al.* (1988) recently reported a high frequency of maternal complications of pregnancy in hypothyroid women: of 16 pregnancies in 14 overtly hypothyroid women, pre-eclampsia occurred in 44%, anaemia in 39%, placental abruption in 19% and postpartum haemorrhage in 19% (among another 12 women with subclinical hypothyroidism, pre-eclampsia was found in 17% and postpartum haemorrhage in 17%). Patients with pre-eclampsia were excluded from analysis in the series of Jones & Man (1969) and not mentioned in the report by Greenman *et al.* (1962), but another eight reports of clinical hypothyroidism in pregnancy (listed in Table 1) include five cases of pre-eclampsia in 19 pregnancies in 17 women. Thus, out of a total of 35 pregnancies in women with overt hypothyroidism, 12 (34%) displayed features of pre-eclampsia. Gestational age at diagnosis of pre-eclampsia ranged from 25 to 42 weeks, and intrauterine death occurred in four pregnancies. It is of interest, none of these patients presented with hypothermia.

The mechanism of pre-eclampsia in hypothyroidism remains to be elucidated. It is unlikely that abnormal thyroid function is one of the causes of true pre-eclampsia but the clinical manifestations of pre-eclampsia (hypertension, proteinuria, oedema) could well be one form of presentation of thyroid dysfunction in pregnancy.

Pre-eclampsia can affect thyroid function, as well. Clinically severe pre-eclampsia is associated with the 'low T3 syndrome' in which low serum T3 concentration is found in clinically euthyroid patients (Osathanondh *et al.* 1976, Tolino *et al.* 1985). A recent study suggests a more generalized disturbance with significant

Table 1. Pre-eclampsia in clinically hypothyroid pregnant women

Authors	Number of			Diagnosis (weeks)		Thyroxine treatment	Fetal outcome
	Women	Pregnancies	PE	PE	Hypothyroid		
Hodges *et al.* (1952)	1	1	0	—	36	AP	1 LB term
Echt & Doss (1963)	3	3	1	25	20, 25, 29	2 AP 1 PP	2 LB preterm 1 LB term (PE)
Anderson & Beales (1970)	1	1	0	—	30	AP	LB term
Lachelin (1970)	1	1	0	—	37	AP	LB term
Kennedy & Montgomery (1978)	1	1	0	—	36	PP	LB term
Boylan & Drury (1979)	3	3	2	36, 42	7, 23, 25	AP, PP	2 LB term 1 IUD 36 weeks (PE)
Blignault (1980)	1	1	1	34	32	AP	IUD 34 weeks
Montoro *et al.* (1981)	6	8	1	29	28	PP	IUD 29 weeks (PE) 7 LB term
Davis *et al.* (1988)	14	16	7	27–41	0–32	13 AP 3 PP	1 Abortion 2 IUD (1 PE) 9 LB term (4 PE) 4 LB preterm (2 PE)

PE = pre-eclampsia.
AP = antepartum. PP = postpartum.
LB = livebirth. IUD = intrauterine death

reduction of total and free T4, as well as elevation of TSH, in pre-eclamptic patients compared with gestational age matched controls (Lao *et al.* 1988b). Rapid changes in thyroid function can occur in pregnancy. This is illustrated by a recent report of a patient with a hydropic fetus who developed pre-eclampsia before delivery, in whom the low T3 syndrome was identified 3 days postpartum (Lao *et al.* 1988a). The explanation proposed was that human chorionic gonadotrophin (hCG), which has thyrotrophin activity (Uchimura *et al.* 1976) and has been implicated as the cause of clinical hyperthyroidism in various pregnancy complications such as molar pregnancy (Hershman & Higgins 1971) and hyperemesis gravidarum (Lao *et al.* 1986, Chin *et al.* 1987), was responsible for the initial hyperthyroxinaemia. After delivery the withdrawal of hCG, coupled with pre-eclampsia, resulted in the low T3 syndrome. In our patient, the clinical picture and sequence of events were multifactorial. The slow progression of hypothyroidism could have been due to partial compensation by the action of hCG. In addition, transplacental transfer of fetal thyroid hormone (Kennedy & Montgomery 1978, Vulsma *et al.* 1989) might also have compensated for failing maternal thyroid function. After delivery, the withdrawal of placental thyrotrophin and fetal thyroid hormone, the effect of pre-eclampsia on thyroid function, as well as the effect of the stress of labour unmasking hypothyroidism, may explain the rapid and dramatic deterioration in thyroid function that occurred 24 h postpartum with development of hypothermia.

Since pre-eclampsia occurs frequently in pregnant women with thyroid disorders, and since in hypothyroid women early detection and treatment may decrease the occurrence of complications and improve the fetal outcome (Echt & Doss 1963), thyroid function tests should become part of the management of pre-eclamptic patients with unusual presentation.

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Placental abruption preceded by abnormal flow velocity waveforms in the uterine arteries. Case report.

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Case report

A 30-year-old pregnant woman was admitted at 26 weeks gestation with hypertension, thrombocytopenia and haemoconcentration. She had had recurrent miscarriages and also placental abruption in five previous pregnancies at 25, 26, 34, 27 and 34 weeks. Only one infant was still alive after an emergency caesarean section at a gestational age of 34 weeks. She was treated with acetylsalicylic acid (80 mg/day) and dipyridamole (75 mg/day) from 12 weeks gestation. Her blood pressure had increased during pregnancy from 120/70 mmHg to 140/100 mmHg. During her admission repeated fetal cardiotocograms showed a normal pattern and ultrasound examination revealed no fetal or placental abnormalities. The pulsatility index (PI) of the umbilical artery was measured several times and stayed within our normal range. Her blood pressure decreased to about 130/90 mmHg but she developed a proteinuria of 1·8 g/24 h.

After giving informed consent, she was included in a research program investigating Doppler ultrasound in abnormal pregnancies. At 29 weeks gestation, Doppler flow velocity waveforms (FVW) were recorded from the umbilical artery, the fetal internal carotid artery and the uterine arteries. The FVWs of the fetal arteries were all within the normal range but the FVWs of the uterine arteries were extremely abnormal (Fig. 1); the PI values were very high in both the right and the left arteries (Fig. 2) and the FVWs showed a pronounced notch. These findings indicate a considerably increased resistance to blood flow in the uteroplacental circulation (Campbell *et al.* 1983). During these observations the uterus was fully relaxed and the placenta showed no abnormalities on ultrasound.

A routine fetal cardiotocogram recorded 20 h later showed a normal heart rate pattern but 8 h later the woman had acute abdominal pain with increased uterine tone and the fetal heart sounds could not be heard. The diagnosis of fetal death by placental abruption was confirmed by ultrasound examination.

She was delivered of a stillborn boy weighing 1100 g (between the 10th and 25th centile). The placenta weighed 322 g and contained a few small infarcts (<10%) and there were a few blood clots on the maternal surface

Comment

In 0·7%–1·17% (Abdella *et al.* 1984, Huisjes *et al.* 1979) of pregnancies the placenta separates preterm from the uterine wall. Perinatal mortality is high, mostly as a result of asphyxia and immaturity. The reported rates varying from 36·5% (Abdella *et al.* 1984) to 55% (Huisjes *et al.* 1979). Much depends on how placental abruption is defined.

The aetiology of placental abruption is unknown but there is an association with maternal hypertension, the condition can be recurrent and rarely is caused by trauma to the pregnant uterus.

Morrow *et al.* (1988) reported pathologic FVWs in the uterine and umbilical arteries shortly after placental abruption. The observations in our patient show for the first time highly abnormal FVWs in the uterine arteries some hours before abruption.

It is not likely that the acetylsalicylic acid or dipyrimadole medication, which were continued up to the time of abruption, has had a direct

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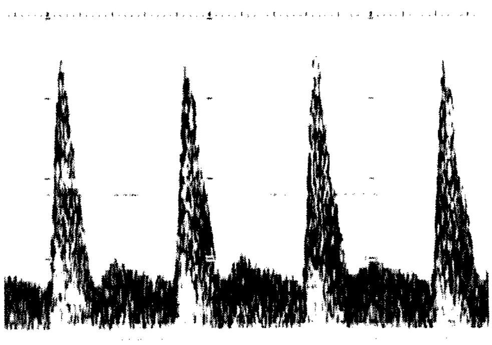

Fig. 1. Flow velocity waveforms of uterine artery; note the pronounced notch.

effect on the FVWs. Such an effect has not been reported and is unlikely in view of the mode of action of these drugs.

It has been suggested that prolonged spasm of the uteroplacental arteries when followed by dilatation results in the rupture in these arteries and consequent retroplacental haemorrhage (Wilkin 1965). The present observations suggest that there is an increased resistance to blood flow in the uteroplacental circulation before placental abruption.

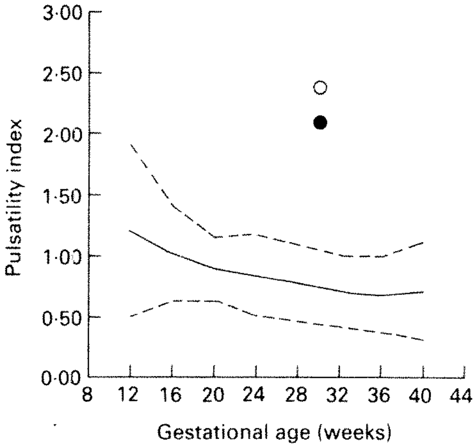

Fig. 2. Pulsatility index of both uterine arteries (● = left, ○ = right) shortly before placental abruption. Values of normal pregnancies are presented as mean ± 2 SD.

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Errata

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Correspondence

The following letters to the Editor should have appeared with ADONIS Index numbers.

Transvaginal pulsed Doppler ultrasound assessment of blood flow to the Corpus luteum in IVF patients following embryo transfer (Torode, Griffiths & Gill). ADONIS 030654569100028C

The effect of caput succedaneum onoxygen saturation measurements (Schram & Gardosi). ADONIS 030654569100029P

Commentary. Detrusur instability—current management (Hosker). ADONIS 030654569100030J

Use of Gynocheck endometrial tissue sampler in infertility (Meekins & Haddad). ADONIS 030654569100031W

Autoimmune ovarian failure with elevated serum levels of lutenizing hormone and enlarged ovaries (Fox). ADONIS 030654569100032B

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ADONIS 030654569100054L

SHORT COMMUNICATIONS

Diplopia after labour. Case report

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Case report

A healthy 33-year-old primigravida with unremarkable medical history had an uncomplicated antepartum course and presented in labour at full term. The second stage of labour lasted approximately 30 min with 20 min of active pushing. Immediately after the birth, she complained of vertical diplopia and retro-orbital pain. The third stage was unremarkable, with spontaneous separation and expulsion of the placenta and complete membranes, and without excessive bleeding (300 ml). Twelve hours after delivery ophthalmological examination showed visual acuity of 20/20 in each eye. Visual fields were full to confrontation. No anisocoria was present and both pupils reacted briskly to light. There was no relative afferent pupillary defect and no abnormality was seen during slit-lamp examination. No redness of the orbital region was present and pain was not elicited by palpation. Hertel exophthalmometry disclosed a non significant difference between the eyes (RE 18 mm LE 17 mm) (Nucci *et al.* 1989). The ocular motility examination showed an impaired RE elevation. A red-glass test disclosed an homonymous vertical diplopia. Standardized B-scan echography showed an extensive, firm, superotemporal extraconal haematoma situated between the periorbita and the superior rectus muscle (Fig. 1a). An A-scan echography showed a low reflective area consistent with haematoma (Fig. 1b).

After 18 days the diplopia resolved and the orbital haematoma cleared on ultrasound examination.

Discussion

Acute orbital haemorrhage can be caused by Valsalva manoeuvre (Katz *et al.* 1985). A small number of women with orbital haemorrhage following labour have been reported by Jackson *et al.* (1988) and by Geyer *et al.* (1990). Like those described previously our patient was a young sportswoman (skier and mountain climber). This seems to be consistent with the hypothesis that women in a high state of physical training can increase abdominal pressure during the

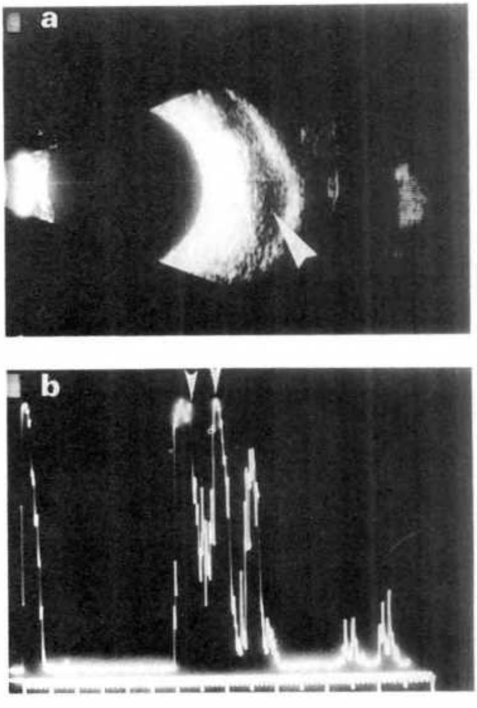

Fig. 1a. B-scan echography showing the orbital haemorrhage (arrow). **Fig. 1b.** A-scan echography showing the low reflective area of the orbital haemorrhage (between the arrows).

Correspondence: Paolo Nucci, Clinica Oculistica dell'Universitá Ospedale S. Raffaele, via Olgettina 60, 20132 Milano, Italy second stage of labour to a greater extent than those who are untrained. Our experience shows the importance of ultrasound in diagnosing and monitoring orbital haematoma and suggests that these women can be safely followed up with this technique. Resorption of haemorrhage is expected. We believe that standardized echography offers clear advantages over computed tomography in observing these patients such as accuracy, specificity, harmlessness and feasibility.

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Patient selection for hysteroscopic endometrial resection

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During the past year the press, both lay and medical, has shown considerable interest in minimally-invasive methods of treating excessive menstrual bleeding. Techniques involving transcervical endometrial resection (Magos *et al.* 1989), endometrial ablation using the neodymium yttrium garnet (Nd-YAG) laser (Davis 1989), electrodiathermy with a rollerball (Vancaille 1989) and endometrial ablation using radiofrequency thermal energy (Phipps *et al.* 1990) have been advocated. Such surgery appears to have tremendous potential benefits, both for patients and the Health Service. When a new technique is introduced, particularly when it apparently has considerable advantages over conventional treatment, there is a danger of overuse, operations being performed when previously a more conservative approach might have been adopted. It therefore becomes difficult to predict the impact the new technology will have on any particular unit.

In an attempt to define accurately the number of patients who might be suitable for endometrial resection instead of hysterectomy for the treatment of excessive menstruation the case records and history reports of all women who had hysterectomies performed under the National Health Service in Leeds Western District between January and June 1988 have been reviewed.

Methods and results

Leeds Western District has six consultant gynaecologists serving a population of 365 000. There are 84 dedicated gynaecology beds. Women who had a hysterectomy between January 1 and June 30 1988 were identified from the computerized histology records and their case notes were reviewed. The indications for hysterectomy were classified using a method similar to that described by Grant & Hussein (1984), except that the histological diagnosis was taken into account in identifying those women with ovarian pathology.

The women who had undergone hysterectomy were, in retrospect, considered to have been suitable for endometrial resection if excessive menstruation was the indication for hysterectomy, in the absence of a concomitant secondary indication for hysterectomy or any significant uterine pathology. Women with leiomyomata less than 1 cm diameter, or with resectable submucous or pedunculated leiomyomata, or super-

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Table 1. Primary indication for hysterectomy in 375 women between January 1 and June 30 1988

Indication	Subtotal	Total number
Excessive menstruation		186
Prolapse		57
Carcinoma		41
Cervix	27	
Body of uterus	8	
Ovary	6	
Pelvic mass		26
Fibroids	14	
Benign ovarian cysts	12	
Premalignant disease		23
CIN 1 plus VAIN 1	1	
CIN 2	3	
CIN 3	13	
Atypical endometrial hyperplasia	5	
Leiomyosarcomatous polyp	1	
Pain		23
Stress incontinence		10
Endometriosis		4
Other		5
Total		375

ficial adenomyosis were not excluded as they could have been treated successfully by endometrial resection (Vollenhoven *et al.* 1990).

A total of 375 hysterectomies were performed during the review period. The primary indications for hysterectomy are shown in Table 1. Excessive menstruation was cited as the main reason for hysterectomy in 186 (49·6%) and in 85 of these (45·7%) no significant histological abnormality was found to explain the abnormal menstrual bleeding.

Applying the criteria outlined above, 108 women were deemed to have been suitable for endometrial resection Of the 186 women who had excessive menstruation 78 were considered unsuitable, most frequently because of the presence of large or multiple leiomyomata (39). Other reasons for unsuitability included urinary incontinence (12), endometriosis (8), cervical intraepithelial neoplasia (7), atypical endometrial hyperplasia (5) and, less frequently, pain, prolapse, an ovarian cyst, a large adenomyotic uterus, and a patient who had previously had a 'Manchester repair' operation.

The 108 women deemed to be suitable for endometrial resection represent 58% of those who complained of excessive menstruation and 29% of all the hysterectomies performed. The mean age of these 108 women was 40.3 years, 63% held regular employment and 45% had children under the age of 14 years. Forty (37%) had evidence of iron deficiency, with or without anaemia and 50% had complained of an irregular (>7 days intermenstrual variation) or shortened (<21 days) menstrual cycle.

The mean uterine dimensions in the women considered suitable for endometrial resection were: longitudinal 9.3 cm (SE 0.15), transverse 5.5 cm (SE 0.12) and anteroposterior 3.7 cm (SE 0.087). The mean uterine weight was 113.1 gm (SE 4.6).

Of these 108 women 49 (45%) had a vaginal hysterectomy and 59 (55%) an abdominal hysterectomy, 21 (19%) had some postoperative morbidity. Infection associated with significant pyrexia (>37.5°C for 24 hours) was found in 11, seven needed further surgery, three during the same admission period and four within the first year after hysterectomy for problems arising from the original operation. Other complications included a wound haematoma, secondary haemorrhage managed conservatively, detrusor instability and deep dyspareunia.

Comment

The operation of hysterectomy is associated with a low mortality rate (Wingo *et al.* 1985) but a significant morbidity rate (Dicker *et al.* 1982), well illustrated in this study. It would appear that endometrial resection, or similar minimally invasive methods, could be used in place of a hysterectomy in up to 58% of patients complaining of menorrhagia. These techniques seem to have considerable financial benefits for the Health Service (Rutherford & Glass 1990) and numerous advantages for patients and the community (Magos 1990), although their long term efficacy remains unproven (Garry 1990).

Although some may regard the criteria for case selection which we used too rigid, we considered it important to identify a well defined group in which we could confidently apply the diagnosis of 'dysfunctional uterine bleeding'. The techniques referred to are new and long term assessment is necessary to determine whether the initial success and safety of the procedure is maintained.

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CORRESPONDENCE

Prediction of pregnancy-induced hypertensive disorders by angiotensin II sensitivity and supine pressor test

Dear Sir,

We were surprised to note the recent re-appearance of the roll-over test for the possible prediction of pregnancy-induced hypertension (PIH), as reported by Dekker *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 817–821] and Schiff *et al.* (1989), in view of the failure of this test to give consistent or clinically useful results, as reviewed by Wallenburg (1989). Our experience may be of interest to others who may seek to identify potential candidates for the pharmacological prevention of pre-eclampsia with low-dose aspirin.

We performed roll-over tests in 62 healthy primigravidae at both 28 and 32 weeks gestation, according to the method of Gant *et al.* (1974). None of the subjects had a past history of hypertension or renal disease, nor was any medication taken other than iron tablets. The results obtained are shown in Table 1. A positive test occurred when the diastolic blood pressure rose by >20 mmHg when the woman rolled-over from the left lateral position to the supine position. PIH was defined as a blood pressure of >140/90 mmHg recorded on two occasions 6 h apart, with a rise in the diastolic value of >20 mmHg, after the 20th week of pregnancy.

In our hands, therefore, the positive predictive value of the roll-over test was 0% when performed at the 'usual' 28 weeks. When repeated at 32 weeks, all the subjects had negative tests despite four patients subsequently developing PIH. We would not, therefore, advocate the continuing use of this test in an attempt to predict PIH.

In addition, a blood sample was taken for estimation of plasma renin concentration by indirect radio-immunoassay, immediately before the roll-over test was performed. No significant difference in plasma renin concentration was observed between the subsequently normotensive and PIH groups, at either gestational age.

We would agree with Dekker *et al* (1990) on theoretical grounds that with the sphygmomanometer cuff placed on the left (upper) arm, an artifactual rise in diastolic blood pressure might be expected when the patient rolls over from the left lateral position to the supine position, as the position of the cuff relative to the heart will be altered. Correspondingly, avoidance of this artefact by placing the cuff on the right arm would be expected to reduce the mean increase in diastolic blood pressure after rolling-over, and it might then be appropriate to choose a new cut-off point to represent a positive test. However, there does not seem to be any reason why changing the cuff arm, and hence recalibrating the test in this way, would afford any better discrimination between 'subsequently normotensive' and 'subsequently hypertensive' groups. In our study, the mean increase in blood pressure after rolling-over was only 2 mmHg.

We believe that other factors may be responsible for the observed variation in roll-over test results between different studies. The age and ethnic origin of the subjects may be important. In our study the mean age was 24 years and three negro women were included in our random sample. The study of Gant *et al.* (1974), which described a 93% positive predictive value, involved very young black teenagers (Gant N. F., personal communication). In addition, methodological variations in the way in which the blood pressures are recorded may influence

Table 1. Prediction of pregnancy-induced hypertension (PIH) by means of roll-over test (ROT)

Test result	Outcome Normotensive (*n* = 58)	PIH (*n* = 4)
At 28 weeks		
Negative ROT	53	4
Positive ROT	5	0
At 32 weeks		
Negative ROT	58	4
Positive ROT	0	0

the results. We used the London School of Hygiene and Tropical Medicine blind-reading sphygmomanometer to avoid digit preference, and Korotkov 4 was used for the diastolic value.

We would suggest that there are problems not only with the roll-over test methodology, but in light of our results, the intrinsic value of the test for the prediction of PIH is negligible in a UK population.

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Reliability of colposcopy and directed punch biopsy

Dear Sir,

In their recent article Skehan *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 811–816] demonstrated a 54% false negative rate in colposcopically directed punch biopsies taken at the time of first assessment when compared with subsequent laser cone biopsies. They concluded that when planning further management the cytological and colposcopical findings should be taken into consideration. We agree.

We were surprised that no mention was made of the referring cytopathology reports, which must surely be an important part of any colposcopy audit. In our experience smears taken at the time of first colposcopic assessment are not only generally inferior to those taken in a primary medical care setting, but are, with few exceptions, a waste of resources.

At Lewisham, since October 1989, we have been using large loop excision of the transformation zone (LLETZ) to both investigate and treat cervical precancer. In our experience the thermal artefact seen in the histopathological specimens produced by LLETZ is far less than that seen with 'laser cones', permitting more accurate analysis by the pathologist. Audit of the data recorded during the first 6 months after the introduction of LLETZ revealed four invasive squamous carcinomas (three microinvasive, one frankly invasive) detected by this method. Our referring cytological false positive rate (using the histological report of the LLETZ as the 'gold standard') was less than 5%; this included eight women with persistent borderline changes or mild dyskaryosis, and a single incorrectly diagnosed severe dyskaryosis from an inflamed atrophic cervix.

In a matched group of patients, treated by laser ablation after a previous colposcopic assessment and directed punch biopsy, the referring cytological false positive rate (using the punch biopsy as the 'gold standard') was 23%; this included four reported as moderate dyskaryosis, one as severe dyskaryosis and one as possible invasion.

It is obvious that sample error makes colposcopically directed punch biopsies less satisfactory than excision biopsy of the transformation zone in the diagnosis of cervical carcinoma and its precursors. Our data serve as a timely reminder that a positive cytology report should not be regarded as incorrect solely on the basis of negative punch biopsy histology.

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References

Skehan M , Soutter W. P., Lim K., Krausz T. & Pryse-Davies J. (1990) Reliability of colposcopy and directed punch biopsy. *Br J Obstet Gynaecol* **97**, 811-816.

Author's reply

Dear Sir,
We are pleased that Carter *et al.* agree with the main thrust of our paper It is important that positive cytology is not ignored either because the punch biopsy is negative or because colposcopy appears to be normal (Ramirez *et al.* 1990).

We made no mention of the referring cytology reports because we do not receive details of those reports in a large proportion of the cases referred to us

W. P. Soutter
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References

Ramirez E. J., Hernandez E. & Miyazawa K. (1990) Cervical conization findings in women with dysplastic cervical cytology and normal colposcopy *J Reprod Med* **35**, 359–361.

British Journal of Obstetrics and Gynaecology
February 1991, Vol 98, p. 233

ADONIS 0306545691000585

Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 IU/l (IRP)

Dear Sir,
We have read with interest the recent publication by Cacciatore *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 904–908]. At Hammersmith Hospital, between September 1988 and December 1989, a total of 160 patients were admitted for suspected ectopic pregnancy. Fifty one of these were not pregnant. Of the 109 pregnant patients at 1000 IU/l (IRP), 41 had intrauterine pregnancies (38%) and three had heterotopic pregnancies (3%). Sixty five patients had ectopic pregnancy, 63 of which were scanned, 55 (87%) by vaginal ultrasound. Two patients, one with a cornual and one with a heterotopic pregnancy were not diagnosed correctly on vaginal scanning. The remaining two heterotopic pregnancies were correctly diagnosed.

The sensitivity of diagnosing ectopic pregnancy by vaginal ultrasound in pregnant patients was 96% and the specificity was 100%. The positive predictive value was 100% and the negative predictive value was 92%.

Our results confirm the findings by Cacciatore *et al.* that when available, vaginal scanning is the most informative investigation in patients with suspected ectopic pregnancy.

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Cacciatore B, Stenman U. H. & Ylostalo P. (1990) Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 IU/l (IRP) *Br J Obstet Gynaecol* **97**, 904-908.

British Journal of Obstetrics and Gynaecology
February 1991, Vol. 98, pp. 234–236

BOOK REVIEWS

Adipose Tissue and Reproduction (Progress in Reproductive Biology and Medicine Vol 14) edited by R. E. Frisch. Karger, Basel, 1990. 142 pages with figures and tables. S/Fr 139, DM 166, £58.00, US$92.75

mens sana in corpore sano—Those out pounding the marathon course or pumping iron in the gym to try to secure a sound body to encase their sound minds might do well to contemplate the following. Women who participate in moderate and regular exercise have frequencies of amenorrhoea between 6% and 43% depending on weekly mileage. Men running more than 65 training km per week have reduced levels of total and biologically available testosterone compared with those running shorter distances.

This is a small volume of reviews on the relation of body fat to successful reproduction, and other aspects of oestrogen activity. The volume editor is Rose Frisch, whose extensive hypotheses on the relationship of body composition to puberty and fertility are well known. The idea that a certain energy reserve as body fat is permissive of human ovulation is attractive and biologically plausible.

Her invited contributors present a series of papers on the relationships of adipose tissue to endocrine function.

Particularly interesting are the reviews of Barbieri on the role of adipose tissue and hyperinsulinaemia in the development of hyperandrogenism, Siiteri on obesity and peripheral oestrogen synthesis, and the related paper of Simpson & Mendelson on the role of adipose tissue in oestrogen biosynthesis in the human. As might be expected in this developing field the impression is of much interesting work still to be performed.

A final comment is on the paper on comparative biology of reproduction in animals, by Thomas from the Department of Zoology of the University of Guelph in Ontario. He describes a continuum of dependency on fat stores for reproduction. At one extreme are species which acquire fat and use it and other body tissues to support reproduction in the absence of feeding, the opposite are species which show little fat build up and meet the needs of reproduction by direct feeding. The examples given with their relationships to breeding seasons and food availability, quantitative and qualitative, are fascinating. It comes as something of a surprise however, to learn that cannibalism of the young by the female may be an adaptive mechanism to adjust litter size to the amount of food available, practised by the wild European rabbit! That wasn't mentioned in *Watership Down*.

For anyone with more than a passing interest in this research area this book is highly recommended although the price seems a little too high for a personal copy.

Robert Fraser

Infertility Surgery. A Multimethod Approach to Female Reproductive Surgery edited by John J. Stangel. Appleton & Lange, Norwalk, Connecticut, San Mateo, Calif. 1990. 396 pages, £83.45. **Tubal Reconstructive Surgery** by Ginter Sotrel. Lea & Febiger, Philadelphia, London. 1990. 281 pages, £51.56.

Dr Stangel's book represents the experience of 24 American gynaecologists, well known and some themselves authors of books on the subject. Dr Sotrel's book is almost entirely his own work, thus avoiding the disadvantages and reduplications of multiple authorship, and enabling him to develop an holistic approach to the whole subject of infertility. Both books, as usual in texts on this subject, are divided into two parts: the first dealing with 'basics', i.e., tubal anatomy, patho-physiology, aetiology and prevention of adhesions, methods of investigation, instrumentation and magnification; and the second with details of surgical technique. Sotrel's chapters on aetiology and pathology of oviductal damage and prevention of postsurgical adhesions are particularly good, whilst in Stangel's book they are sandwiched between the two sections, of some 60 superbly written pages, by Ronald Batt on endometriosis.

Surgical techniques for reconstructing

blocked tubes, including, inevitably, reversal of sterilization, are well described in both texts with excellent diagrams. Unfortunately, the photographs in both are only in black and white and are disappointing in comparison with those in other books on the subject.

So, how do these two volumes compare with the well-known texts of the last decade, and what is new in reproductive surgery? Hysteroscopy, wider use of operative laparoscopy and laser surgery are the answer. Daniell & Martin on laparoscopic laser surgery make thoughtful and informative contributions in Stangel's book, as do Neuwirth & Corson on hysteroscopic surgery. Unfortunately, in this rapidly developing field, there are few references to work done or results obtained later than 1985.

The conservative management of ectopic pregnancy is well presented in both, but the use of vaginal ultrasound as a diagnostic tool and the frequent occurrence of heterotopic pregnancy in assisted reproduction are striking omissions. Sotrel accepts ovum transmigration as explanation for the frequent finding of a corpus luteum contralateral to the tubal pregnancy, and there is no mention of Iffy's reflux theory and its more plausible explanation of this and other anomalous features in the natural history of tubal pregnancy. Laparoscopic methods of treating polycystic ovarian disease are not mentioned in either text.

Otherwise there is little new to add to the well-known microsurgical techniques described by previous authors. Salpingoscopy is described by Sotrel, but its impact on selecting patients suitable for tubal surgery is not yet assessed.

Both books have excellent lists of references at the end of each chapter. Sotrel's are more up to date and more comprehensive; he discusses in greater detail the aetiology and pathology of tubal occlusion at different sites and, in his book, these are well illustrated by hysterosalpingograms. However, few European gynaecologists would agree with him that endometriosis is the commonest cause of distal tubal occlusion. Uterine reconstructive surgery is well illustrated in both texts. Myomectomy is better described by Stangel who advocates preoperative treatment with GnRH analogues as well as local vasopressin injections at the time of operation.

A text on infertility surgery is not the proper place for describing IVF techniques but a critical assessment of the role of and the indications for either technique should be an integral part of any modern book on this topic. Stangel's book fails to attempt a comprehensive review of the subject, although there are brief references to it scattered throughout various chapters. This subject is tackled more satisfactorily in Sotrel's final chapters on the evaluation of surgical results and alternatives to tubal surgery.

Both these books are worth purchasing: Stangel's with descriptions of alternative surgical techniques should find a place in the departmental library. Sotrel's more wide ranging book which includes discussion on subjects such as effect of age on fertility, relation of IUCDs to pelvic infection, techniques of tubal sterilization, bacteriology of salpingitis and second look laparoscopy should be in the possession of all who practise infertility surgery.

Herbert Reiss

The Infectious Diseases of the Female Genital Tract. Second edition by Richard L. Sweet & Ronald S. Gibbs. Williams and Wilkins, Baltimore, London, 1990. 494 pages with figures and tables, £59.00

In the five years since the publication of the first edition of this book, much progress has been made in the field of female genital infection. These changes are well reflected in the second edition which provides a current and comprehensive overview of the subject.

The text is well laid out, beginning with an introduction comprising a brief summary of relevant microbial agents, followed by a short review on methods of diagnosis. Thereafter the text deals with specific organisms, a chapter being devoted to each group of organisms. The following section classifies infection clinically, thus providing easy access for the clinician managing a specific clinical problem. Finally, antimicrobial agents and prophylaxis are discussed Inevitably there is a degree of overlap, but the authors have minimized this.

Whilst there is no shortage of comprehensive texts related to sexually transmitted diseases and genitourinary medicine, to date this is the only textbook written by gynaecologists for gynaecologists. Management is described within the context of gynaecology, rather than genitourinary medicine, albeit with reference to current American practice.

With the ever increasing pace of medical research many texts suffer from being out of date by the time they appear in print, this is a problem particularly in the field of AIDS. The authors have included references up to 1988 and, whilst knowledge of HIV has increased greatly since then, the authors have still provided a clinically relevant and scientifically apposite chapter.

This text can be recommended for both the busy practising clinician and as a reference book for those with a more specific interest in female genital tract infection. The authors have produced an informative, highly readable and clinically relevant text.

J. Richard Smith

Books received some of which may be reviewed at a later date

Clinical Gynaecological Oncology second edition edited by John H. Shepherd & John Monaghan. Blackwell Scientific Publications, Oxford, 1990, 479 pages fully illustrated, £59.50

Marshall's Physiology of Reproduction Volume 2 Reproduction in the Male Fourth edition edited by G. E. Lamming. Churchill Livingstone, Edinburgh, 1990, 996 pages fully illustrated, £95.00

Hematologic Disorders in Maternal-Fetal Medicine edited by Murray M. Bern & Fredric D. Frigoletto Jr. Wiley/Liss, New York. Chichester, 1990, 709 pages with figures and tables, $149.95

Human Prenatal Diagnosis Second edition edited by Karen Filkins & Joseph F. Russo. Marcel Dekker Inc, New York, 1990, 624 pages illustrated, $150.00 (US and Canada), $180.00 all other countries

Controls of Sperm Motility: Biological and Clinical Aspects edited by Claude Gagnon. CRC Press, Boca Raton, Ann Arbor, Boston, 1990, 396 pages with figures and tables, £78.00

Atlas of Ultrasound Measurements edited by Barry Goldberg & Alfred B. Kurtz. Year Book Medical Publishers Inc Chicago, London Boca Raton, 1990, 462 pages fully illustrated, £68.00

Controversies in Obstetrics and Anaesthesia No 1 edited by Barbara Morgan. Edward Arnold, London 1990, 138 pages with figures and tables, £16.95 paperback

Student Notes: Obstetrics and Gynaecology Fourth edition edited by James Willocks and James P. Neilson. Churchill Livingstone, Edinburgh, 1990, 324 pages with figures and tables, £9.95

Preparation and Revision for the DRCOG by Janice Rymer, Gregory Davis, Adam Rodin & Michael Chapman. Churchill Livingstone, Edinburgh, 1990, 384 pages illustrated, £14.95 paperback

Uterine Function: Molecular and Cellular Aspects edited by Mary C. Carsten & Jordan D. Miller. Plenum Press, New York and London, 1990, 605 pages with figures and tables, $125.00

Midwifery Practice. Postnatal Care: A Research-Based Approach edited by Jo Alexander, Valery Levy & Sarah Roch. Macmillan Education Ltd, Basingstoke, 1990, 179 pages with figures and tables, hardcover £40.00, paperback £11.99

Obstetric Genetics by Zoltan Papp, Akademiai Kiado, Budapest, 1990, 650 pages, illustrated, $69.00

Proceedings and Symposiums

Why We Eat and What We Eat (Proceedings of the Twelfth British Nutrition Foundation Annual Conference June 1990) edited by Margaret Ashwell. Available from British Nutrition Foundation, 15 Belgrave Square, London SW1X 8PG

Contraception and Mechanisms of Endometrial Bleeding edited by C. D.'Arcangues, I. S. Fraser, J. R. Newton & V. Odlind (Proceedings of a symposium organized by the Special Programme of Research Development and Research Training in Human Reproduction of the World Health Organization 1988) Cambridge University Press, Cambridge, 547 pages, £67.00

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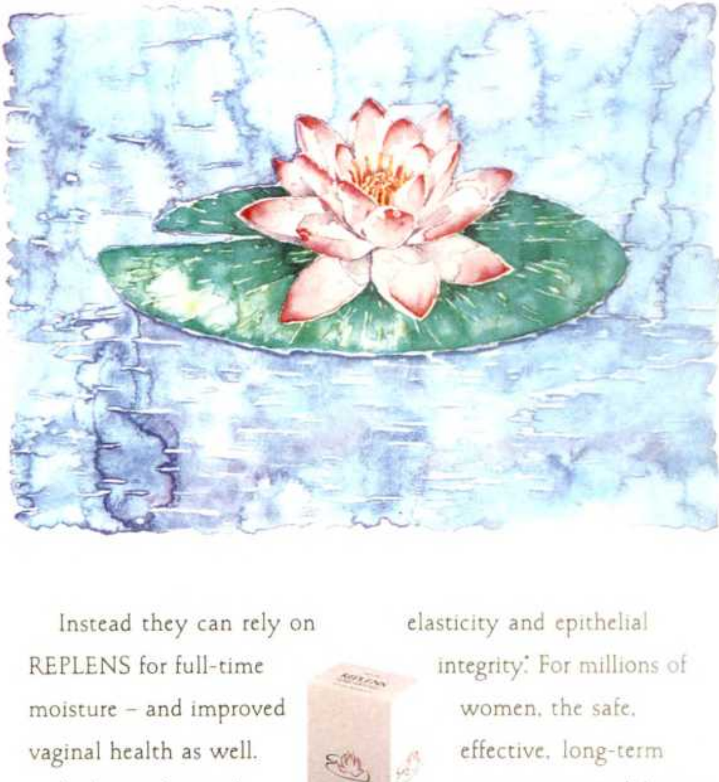

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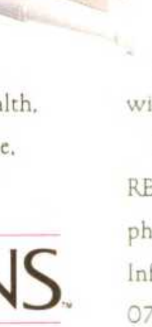

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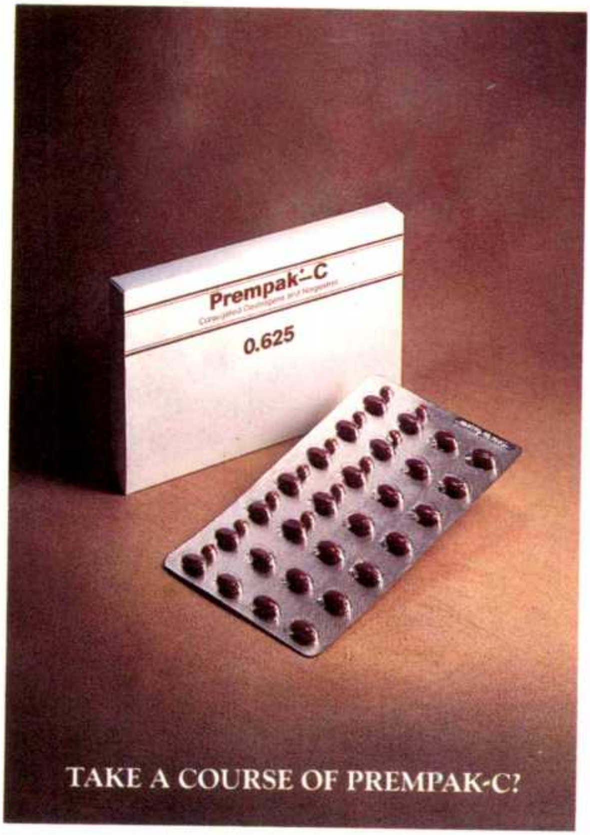

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ADONIS 030654569100059I

COMMENTARIES

The future obstetrician/gynaecologist

What's wrong with our speciality? Something must be amiss if the fall in recruitment, static percentage of women consultants (DHSS 1988) and general dissatisfaction (Francis 1987) are anything to go by.

Demographic change, falling morale in the NHS, increasing demands for reasonable hours by junior doctors and the fear of litigation mean that we must reorganize the structure of our speciality if it is to remain attractive to medical students and junior doctors and to maintain or improve standards of patient care. We have to compete with other specialities for graduates who are voting with their feet. Doctors anticipating working in the 21st century want more than is presently on offer.

Can the haphazard training available now really be called a programme? 'Trainees' have to move round the country, changing jobs frequently, relying on references and patronage for successive posts (Allen 1988). They have little time for study, social or family life, while obsessively completing log-books and casebooks that require too much minor detail. The specialist qualification, the MRCOG, is an entry examination to higher training, rather than an exit accreditation. Obstetrician-gynaecologists remain 'junior' until the age of 38, or later, having learnt by osmosis, with little formal assessment of skills, no curriculum, few trained teachers, no critical forum for debate and challenge and no proper support for the emotional turmoil that the work demands Can one find a description of the expected capability of a trained person? Does training really need to last as long as it does?

There are lessons to be learned from other specialities where integrated training schemes have been developed. In general practice, for example, training revolves around clear aims and objectives. Trainees settle into an area. They have half-day release for lectures, seminars, case discussions and support. They participate in their own teaching and work together for exams. They have some independence from their consultants and can complain, for example, if a hospital job is entirely service work and does not equip them to deal with general practice problems. When we notice that SHOs in general practice training schemes are better than our own, or DRCOG candidates that are as good as those sitting the MRCOG, is it not time to copy a good idea?

Although the details would have to be discussed, the essential features of such a scheme would be:

(1) Shortened planned training (4 years maximum); so that a consultant could be appointed at about 30: This could be achieved by well-thought-out regional rotations. Limited time would concentrate the minds of teachers and trainees alike to maximize the specialist skills and use of clinics and facilities efficiently. The scheme should cover training from SHO entry to accreditation at the end. Unsuitable applicants or those who changed their minds could take the DRCOG after 6 months to a year and leave a scheme.

(2) The objectives of training should be detailed, not in terms of years to gain accreditation, but in breadth and depth of experience and skills obtained. The assumption that, given enough time, every trainee will encounter every problem, and become competent to deal with it, is incorrect. The MRCOG would then supplement these objectives and could be taken mid-way. The MRCOG system itself might change, with examination of the basic sciences and a clinical assessment after 2 years, and presentation and discussion of a modified case book for accreditation at the end.

(3) Improved teaching methods: At regional level, large groups of trainees would make feasible the organization of high-quality lectures and seminars and the use of new technology, such as videos and simulators, for teaching surgical techniques. It is vital to harness and disseminate the experience of our senior consultants, who would thus become accessible to more trainees.

(4) The College might approve the appointment of regional programme directors with responsibility for all the trainees in their area. Their role

would be quite different from the present regional advisor or district tutor and would require imaginative and committed teachers. Such programme directors will need the cooperation of their hard worked colleagues and must be given the power to ensure that trainees attend special clinics, perform enough major surgery or receive half-day release. They could negotiate with other specialities in the region and offer trainees a variety of posts for the elective year (the most singular and distinctive part of our postgraduate education).

(5) There has to be acccountability: of the training programmes to the trainees; and the programme directors, to their fellow consultants, trainees and the College.

If a small number of such fast-track fixed-length programmes were set up now, with College approved accreditation at the end, they would appeal to many juniors, and especially women. Pressure would develop for other regions to follow suit. With sufficient numbers in a scheme, it would be possible to have the flexibility to allow for maternity leave and for a small number of part-time trainees. Sub-specialization could be developed after completion of training, or even later, during the consultant years. Instead of 2 years research, an MD and a long list of publications being virtually obligatory, the elements of critical reading, and involvement in small projects could become part of training. Research posts would then be taken up by those with the necessary ability, enthusiasm and commitment. Applicants for clinical appointments should be asked to list no more than three publications with a brief description of their merits.

Specialist posts

Changes in consultant posts are inevitable (DHSS 1987). There are moves, in the interests of patient care, for increased consultant accountability, a higher consultant to trainee ratio and increased on-call for consultants. A concentrated training programme with early consultant appointment could be supplemented by a system of junior and senior consultant posts, with differential day and night workloads. A more formal system could be established so that experienced colleagues could support junior consultants, even between hospitals. If consultants are to be expected to stay in hospitals and have an increased presence at night-time emergencies, the College must negotiate many more posts soon so that rotas can be reasonable, or else our speciality is going to become peculiarly unattractive. Reducing the age of attaining consultancy will automatically boost numbers.

Short-term contracts of 5–10 years are proposed. The advantages may be flexibility, development of special skills, audit, and open movement into academic work or private practice. Development of different specialist skills within a department will encourage intra-department referrals, foster professional modesty and cooperation and could aid the process of keeping up-to-date. There should be a continuing process of education, or re-certification which would complement changes in training programmes (Brudenell 1989). Reassessment of junior doctors' duties would reveal that midwives and specialist nurses might perform many more tasks, have limited prescribing rights and refer directly to consultants. More obstetric care could be provided by midwives and and general practitioners. Pre-operatively, the surgeon could obtain consent and the anaesthetist assess fitness. More day-to-day consultant care in the wards would compensate for the cross-speciality cover.

Attitudes to women

The profession has finally accepted that it has got to DO SOMETHING, not just to increase the proportion of women entering, but to retain them to reach the top. Part-time and job-sharing (suddenly fashionable) may be a short term solution, and necessary for some women while their children are small, but they are not the whole answer. Such expedients are cosmetic and alone will not be enough. Men, as well as women, want reasonable workloads and remuneration. Intelligent women do not want second class posts, such as the associate specialist without status or responsibility, nor prolonged training, although these may be necessary compromises. Tinkering with the training system could help a few women but a radical overhaul would benefit all the trainees, and would also increase the availability of women specialists. This is what women patients want (Areskog-Wijma, 1987) and the College should have a stated aim of at least 50% women consultants.

We also have to grasp the nettle of misogyny and root it out. Why is there a self-perpetuating male subculture? (Rogers, 1988). Students and patients still tell stories of obscene remarks or of sexist or patronising gynaecologists, and we should be desperately concerned about this image (and the reality). There appears to be a general reduction of trust in all medical practitioners, evidenced by an increasing interest in alternative therapies, and readiness to litigate, and this loss of faith can be felt especially in obstetrics and gynaecology. The doctor-patient relationship would be strengthened by increased respect, so that women sense that they are advised and treated as they wish by an advocate rather than controlled by an elder or better.

Why have much-needed reforms in the training of juniors and the workload of consultants been delayed? This may result partly from the profession being unable to come to terms with the pain and losses entailed by many years of training, the broken sleep and broken relationships, the compromises made and the continued exposure to patients' suffering. Service provided by personal sacrifice is outmoded and is not proven to be in patients' best interests. It leads to criticism of individuals who do not succeed for 'not having what it takes'. Tired and cynical consultants ought not to make the system repay what it has taken out of them. Too many obstetrics and gynaecology departments (notwithstanding dedication and hard work) are unhappy places, due to problems such as demarcation disputes or a difficult, ill or idiosyncratic colleague. Like all abuse, the repeating cycle of lack of care of trainees and colleagues alike continues. We should face the toll that the present training, work-load, and conflicting pressures exact. The work should be satisfying and even joyous, which, after all, was the initial enticement.

Ironically, it may be that pressure from the Government, consumer movements and lawyers will bring the women and men in the speciality closer together. However, we have a choice: to be positive and initiate overdue change, or to retreat to the labour ward bunker crying in vain 'leave the status quo alone'. We must use this opportunity to be constructive.

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Blood pressure measurement in pregnancy

Blood pressure is, or should be, always measured whenever patients attend antenatal clinics, making blood pressure measurement one of the most frequently used screening tests in pregnancy, its object being to detect patients who are developing hypertensive diseases of pregnancy. Yet even casual observation of medical and non-medical staff, using conventional sphygmomanometry, shows that there is wide variation in blood pressure measurement techniques and the report from Birmingham by Perry *et al.* published in this issue of the Journal (p. 241), describes this variability in one hospital.

Recommendations for the measurement of blood pressure with specific comments about pregnancy have been made by a working party of the British Hypertension Society, and published by Petrie *et al.* (1986 and 1990). Predictably the Birmingham workers found that clinicians rarely used a large cuff and were variable in their use of K_4 (muffling of sounds) or K_5 (disappearance of sounds) for the assessment of diastolic blood pressure. The Hypertension Society booklet

(Petrie *et al.* 1990) recommends having two cuffs available with inflation bladders 35 cm wide for normal use and 42 cm wide for use in large arms. The length of the bladder should be at least 80% of the arm circumference. The larger cuff should often be used since errors are likely to be greater using too small a cuff than using one too large.

There is justifiable confusion about the use of K_4 or K_5. For simplicity the Hypertension Society recommends the use of K_4 in pregnancy (Petrie *et al.* 1990) since occasionally and in pregnancy in particular the Korotkoff sounds may be heard with no inflation pressure in the cuff at all. The most rigorous comparison of intra-arterial and sphygmomanometer pressure measurements made in pregnancy (Raftery & Ward 1968) suggests that the use of K_4 over-estimates diastolic blood pressure by 11 mmHg whereas K_5 over-estimates diastolic blood pressure by 7 mmHg. In theory therefore it would appear to be more sensible to use K_5 in pregnancy rather than K_4, reserving K_4 for the relatively few cases where there is no audible K_5 (sounds audible to zero pressure) and noting that K_4 has been used However, this seems excessively complicated and the difference between K_4 and K_5 is usually not large. In practice, consistency with measurements made at other times in pregnancy is more important than the absolute level recorded and this was the reason why the British Hypertension Society recommended the use of K_4 in pregnancy.

Of course it would be more logical to rely on systolic blood pressure measurement rather than diastolic blood pressure. Not only can this be measured more accurately, but also and perhaps consequentially systolic blood pressure is a better predictor of fetal outcome (Tervila *et al.* 1973). But it seems unlikely that the ingrained habits and clinical trial data of many generations will be overturned in favour of systolic rather than diastolic blood pressure.

Perry *et al.* found that blood pressure was measured with the pregnant woman in a variety of postures. The British Hypertension Society recommends the sitting or left lateral position rather than lying supine because of the profound fall in blood pressure that occasionally occurs in late pregnancy due to obstruction of the inferior vena cava. It is also important to note that the sphygmomanometer cuff should be approximately level with the heart; if it is not, as when measurements are made in the upper or lower arm in patients lying in the lateral position, the recorded pressure will be artifactually lower or higher because of the hydrostatic effect of the column blood above or below the heart The effect is smaller when the lower rather than the upper arm is used (Kinsella & Spencer 1989).

Another source of worry from the Birmingham survey was the measurement of blood pressure to the nearest 10 mmHg. If the sphygmomanometer blood pressure was recorded as 90 mmHg the real sphygmomanometer blood pressure could be as low as 85 mmHg or as high as 95 mmHg. The comparison of intra-arterial and sphygmomanometer blood pressures gave 95% confidence limits for K_5 of +28·2 to −6·0 mmHg. Therefore a diastolic blood pressure recorded as 90 mmHg (to nearest 10 mmHg) could be as high as 128 mmHg or as low as 74 mmHg; a range which for an outpatient would encompass admission for urgent delivery (128 mmHg) or sending home with no comment (74 mmHg).

Most clinicians are aware of the unreliability of single estimates of blood pressure and the necessity to consider the whole clinical picture, but the findings of the Birmingham group suggest that this unreliability is worse than necessary. A blood pressure measurement technique standardised in each hospital and ideally throughout the country would decrease some of these errors and make the measurements of blood pressure more worthwhile.

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Conflicting views on the measurement of blood pressure in pregnancy

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Summary. Current practice with regard to the technique of blood pressure measurement in pregnancy was assessed by means of a self-completed questionnaire sent to all midwives (116) and obstetricians (11) working in a UK District General Hospital obstetric unit. The response rate was 72% (91 respondents). Over half of the respondents (53%) use the fifth phase diastolic end point (contrary to current recommendations). Of the 75 respondents who had access to a large adult cuff 54 (72%) had used it on 'less than two occasions' over the preceding four weeks. Only 10% (9) of respondents reported that they record blood pressure to the nearest 2 mmHg and 23% (22) reported that they round blood pressure readings to the nearest 10 mmHg. There were diverse views on the interpretation of multiple blood pressure recordings. The conclusion is that compliance with current recommendations on blood pressure measurement technique in pregnancy is poor. There is poor agreement among midwives and obstetricians as to how blood pressure should be recorded in pregnancy.

The detection and management of the hypertensive disorders of pregnancy has become a major focus of antenatal care. Consequently, measurement of blood pressure is an important antenatal screening test. The predictive value of blood pressure recordings depends largely on minimizing measurement error. Failure to standardize technique will inevitably increase both error and variability in measurement. Detailed recommendations on blood pressure measurement technique that address these issues have been proposed (Petrie *et al.* 1986; Kirkendall *et al.* 1980).

The position of the person in whom blood pressure is measured is important in pregnancy. The supine and right lateral positions are not recommended in view of the effect of the gravid uterus on venous return. The current consensus on the diastolic end point in pregnancy favours the point of muffling of Korotkoff sounds, the fourth phase, whereas the point of disappearance of sounds, the fifth phase, is recommended in non-obstetric practice (Davey & MacGillivray 1988; Petrie *et al.* 1986; Kirkendall *et al.* 1980). In non-pregnant individuals the extent to which blood pressure is overestimated as a result of using a sphygmomanometer cuff of inadequate size relative to arm circumference is increasingly recognized (Linfors *et al.* 1984).

The aim of the present study was to determine

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current practice with regard to the measurement of blood pressure in pregnancy among midwives and obstetricians working in a UK district general hospital.

Method

A questionnaire on blood pressure measurement technique was sent to all qualified midwives, both hospital and community based (116), and obstetricians (11) attached to the Dudley Road Hospital obstetric unit (Table I). More than one response to the question on position was allowed. In all of the remaining questions one response to the range of options was obtained. Additional data on the respondents year of qualification, location of work and grade were also obtained. The response rate, following repeat mailing to non-respondents, was 72% (91 respondents).

Results

Most of the respondents (89%) reported that they usually measure blood pressure in the seated position. The lying position was regarded as suitable for the measurement of blood pressure in pregnancy by 40 (44%) with 33 (36%) indicating that they usually measured blood pressure in both the seated and lying positions. The left lateral position was favoured by 18 (20%), the right lateral by 12 (13%) and standing by one.

All hospital-based staff reported that they had access to a large adult cuff, whereas 16 of 18 community midwives reported that they did not have access to a large cuff. In the four weeks preceding the questionnaire only four of the 75 respondents (5%) who reported access to a large cuff had actually used one on more than six occasions and 54 (72%) had used it on 'less than two occasions'.

Table 1. Details of blood pressure measurement technique questionnaire

Patient position (sitting, standing, lying, right lateral, left lateral).
Access to large cuff (Yes/No)
Frequency of large cuff use over previous 4 weeks (<2, 2–6, or >6 occasions
Diastolic end point used (muffling or disappearance of sounds)
Desired precision of measurement (to nearest 10, 5, 2 mmHg)
If blood pressure elevated at first recording, how many repeat recordings (0, 1, 2, 3)
Recording acted upon (lowest, highest, average, final)

Respondents were divided almost equally on the use of the fourth phase or the fifth phase diastolic end point, ($n = 43$ and 48 respectively). Those favouring fifth phase tended to be more senior in terms of years since qualification: mean 14·5 (SD 8·6) years *vs* mean 11·1 (SD 8·9) years, mean difference 3·4 years, 95% CI −0·2 to 7. Most of the 91 respondents (66%) reported that they measured blood pressure to the nearest 5 mmHg (despite the fact that sphygmomanometers are calibrated to 2 mmHg) and a substantial minority (24%) reported that they recorded blood pressure to the nearest 10 mmHg.

If the initial blood pressure reading was elevated, 50 respondents (55%) reported that they repeated the reading on one occasion with 35 (38%) and four repeating it on two and three occasions respectively. No clear pattern as to which reading respondents acted upon emerged with 13 (16%) of respondents to this question favouring the lowest, 21 (26%) the highest, 19 (23%) the average and 28 (34%) the final recording.

Discussion

There were clearly divergent views as to how blood pressure should be measured and on the interpretation of multiple measurements within our obstetric unit. Compliance with published recommendations, particularly with regard to the use of the large adult cuff and the appropriate diastolic end point, was poor. The lack of a uniform diastolic end point in pregnant and non-pregnant subjects is a likely cause of confusion on the latter issue.

The finding that 44% of respondents report measuring blood pressure in the vaguely defined 'lying' position and 13% in the right lateral position, suggests a low level of awareness of this important source of blood pressure variability in pregnancy.

Confusion and uncertainty regarding blood pressure measurement technique are not confined to obstetric practice (Taylor *et al.* 1979) and are unlikely to be unique to this unit. The findings highlight the need for obstetric units to formulate a clear policy on this important practical issue. The relevant staff in our unit will receive feedback on the results of this survey and a uniform blood pressure measurement technique will be adopted. This study has provided valuable audit data for our obstetric unit and we suggest that the simple methodology employed may usefully be extended to other areas of practice.

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The prevention of the maternal manifestations of pre-eclampsia by intensive antihypertensive treatment

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Summary. The purpose of the study was to determine if reduction of pregnancy hypertension to normal prevented the clinical maternal manifestations of pre-eclampsia. Thirty-six women with hypertension, but without proteinuria, were allotted at random to a test group of 17 who received intensive treatment, and a control group of 19 who were managed according to routine methods by hospital staff unconnected with the study. The development of proteinuria was chosen as an indicator of pre-eclampsia. Proteinuria developed significantly more often in the control group (in six of the 19 women) than in the test group (in one of the 17 women).

Hypertension in pregnancy, irrespective of aetiology, may be complicated by pre-eclampsia in late pregnancy. The maternal clinical manifestations of pre-eclampsia (De Swiet 1985; Weinstein 1982; Davies *et al.* 1980; Killam *et al.* 1975; Ferris 1984; Bonnar *et al.* 1971) such as proteinuria, oedema, cerebral irritation, microangiopathic haemolytic anaemia, disseminated intravascular coagulation, thrombocytopenia, hepatic dysfunction and hyperuricaemia are reminiscent of the complications that may occur with accelerated hypertension unassociated with pregnancy (Kaplan 1980: Leading Article 1981). In accelerated hypertension these complications are usually accepted as being due to hypertension and it seems possible therefore that the clinical maternal manifestations of pre-eclampsia may also be solely the result of hypertension, whether this arises de novo in pregnancy (pregnancy-induced hypertension) or as an exacerbation of a pre-existing hypertension (pregnancy-associated hypertension). If this hypothesis is correct then control of the hypertension should prevent the maternal manifestations of pre-eclampsia. This was the basis of the present study.

Proteinuria was chosen as an indicator of pre-eclampsia since it is a constant feature, and represents a readily-definable end-point. To date no consensus has emerged as to whether or not control of hypertension in pregnancy prevents proteinuria (Rubin *et al.* 1983; Redman *et al.* 1976; Gallery *et al.* 1985; Collins *et al.* 1985; Mabie *et al.* 1986; Arias & Zamora 1979). It is noteworthy that in most studies, the aim of therapy was to reduce the blood pressure below the upper limits of an arbitrary normal range, but not necessarily down to normal levels (Rubin *et al.* 1983; Gallery *et al.* 1985; Mabie *et al.* 1986; Arias & Zamora 1979). The object of this study was to determine if, by reducing the elevated blood pressure (whether pregnancy-induced or pregnancy-associated) to as near the average normal as possible, the development of pre-eclampsia as manifested by proteinuria could be prevented.

Subjects and methods

Women whose blood pressure was 140/90 mmHg or more, on two separate days, without proteinuria, were recruited to the study from the

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antenatal clinic. Those who had reached 38 weeks gestation, or who lived too far from the hospital to attend for frequent examinations were excluded. Blood pressures were measured by medical staff with a standard sphygmomanometer, the diastolic pressure being taken at the 5th phase.

After recruitment, the women were randomly allocated to one of two groups, test and control, by simple randomization. For this purpose cards marked 'Test' or 'Control' had been prepared in advance in equal numbers, and sealed in identical envelopes. These were shuffled into random order and then numbered in sequence. As each woman was recruited the envelope next in order was opened to determine assignment, thus avoiding any element of choice or control by the investigators. All the women in the test group gave informed consent.

In determining the number of women required for the study, the frequency of proteinuria in pregnancy hypertension was reckoned to be in the region of 30% ($P_1 = 0{\cdot}03$), while the desired effect of treatment was the prevention of proteinuria in all the women ($P_2 = 0{\cdot}0$). Under these circumstances a sample size of 50 (25 in each group) or 36 (18 in each group) would afford 90% and 80% power, respectively, to detect statistically significant differences ($P = 0{\cdot}05$) between the groups. Since the total elimination of proteinuria in the test group seemed an excessively ambitious target it was decided to recruit 60 patients, affording an 80% power to detect a significant difference even if 5% ($P_2 = 0{\cdot}05$) of the test group developed proteinuria. The trial was initially approved by the hospital ethics committee, but later, when a total of 36 patients had been studied, the committee recommended that the study be concluded because of possible adverse effects of treatment on placental blood flow (see Discussion).

The test group was treated with atenolol, methyldopa and bendrofluazide with the aim of reducing the blood pressure as near as possible to the average normal level for that stage of pregnancy. Therapy was commenced with either 50 mg daily of atenolol or 250 mg three times daily of methyldopa, the choice depending in many instances on the presence of ancillary features such as anxiety or tachycardia (when atenolol was chosen), or airways obstruction (when methyldopa was chosen). The drug dosage was gradually increased, as required, to a maximum of 750 mg three times daily of methyldopa or 100 mg daily of antenolol. Where monotherapy proved inadequate, the two drugs were combined. In the minority who failed to respond fully to this combination, bendrofluazide 2·5 mg, in a potassium-combined tablet, was added as a third agent, increasing as necessary to 5 mg daily. Women were routinely checked at weekly intervals, but twice weekly in instances where control was unstable.

It was considered unethical to withhold hypotensive therapy from women in the control group, and they were managed according to customary hospital practice by medical staff who were unconnected with the study. This management involved less intensive treatment than was used in the test group, since there was lack of conviction about the value of hypotensive drugs, especially in the milder cases. The only hypotensive drug administered was methyldopa and in many instances no drug was used. In general the aim of treatment was to reduce the blood pressure below 140/90 but not necessarily down to the normal level.

In both test and control groups, nursing staff, unconnected with the study, routinely tested for proteinuria by dipstick (Ames reagent strips). Where proteinuria was found it was confirmed by the sulphosalicylic acid test. A +1 or more, in the absence of urinary tract infection, was regarded as confirmation of proteinuria.

For the women who developed proteinuria, the trial terminated at that point, while for those who did not develop proteinuria the trial terminated at delivery. In either case the outcome of delivery was monitored in all women from the perspective of both mother and child. In order to adjust birthweight for gestational age, standardized nomograms for Irish newborn male and female children were used (Hayes *et al.* 1983).

For comparison between groups the following statistical techniques were applied as appropriate: Student's *t*-test (two-sample) for continuous data; the χ^2 test or Fisher's exact test for categorical data of an interval nature; and the Wilcoxon rank sum test for comparison of medians as in the Apgar score. Statistically significant difference implies $P<0{\cdot}05$.

Results

Of the 36 subjects, 17 were randomized to the test group and 19 to the control group. There were no withdrawals from the study. The two groups were well matched with respect to age, parity, blood pressure and the proportions with pregnancy-induced and pregnancy-associated hypertension (Table 1). The effect of treatment on blood pressure is shown in Table 2.

Proteinuria developed in one of the 17 women in the test group and in six of the 19 in the control, a statistically significant lower frequency in the test group (Table 3). Table 3 also presents the result of treatment on outcome. There were no significant differences between the two groups in Apgar scores, gestational age at delivery or perinatal deaths (two in the test group and one in the control group). However, the mean birthweight was significantly lower in the test group and a significantly higher proportion of the babies in the test group had a birthweight below the 50th centile for gestational age, as established for Irish newborns at the same hospital (Hayes *et al.* 1983; Gallery *et al.* 1985; Fidler *et al.* 1983).

Discussion

Methyldopa has for long been regarded as relatively safe in the treatment of hypertension in pregnancy. More recently, a number of studies have attested to the safety of atenolol and other beta-blockers, (Rubin *et al.* 1983; Sandrom 1978; Thorley *et al.* 1981; Lardoux *et al.* 1983; Gallery *et al.* 1985; Fidler *et al.* 1983). Controversy surrounds the use of diuretics, on the basis that as the blood volume is already reduced, a further reduction might have an adverse effect on the fetus. No convincing evidence for this hypothesis has ever been produced (Ferris 1984, Collins *et al.* 1985). A reduced blood volume is common in most kinds of hypertension, including essential hypertension, and may well be due to a primary reduction in the calibre of the vascular compartment rather than a relative reduction in blood volume (Ferris 1984). Under these circumstances, a thiazide diuretic was administered during this study where the hypertension failed to respond adequately to a combination of methyldopa and atenolol.

In spite of this intensive therapy, a normal blood pressure was not achieved in the test group as a whole (Table 2). It was not possible to do so without risking occasional hypotension, but the result was appreciably better than achieved by standard hospital treatment in the control group. Pregnancy hypertension is often difficult to control. It may be highly resistant to treatment, frequently requiring multiple drug therapy. It seems to be rather labile, exhibiting unexpected surges in severity during which pre-eclampsia may supervene within as short a period as 48 to 72 h of poor control.

Our results suggest that intensive treatment of hypertension in pregnancy may prevent the maternal manifestations of pre-eclampsia. Proteinuria occurred less often in the test group and seems to be a product of the hypertension and not a manifestation of renal damage from some other mechanism. The pathogenesis of the proteinuria would appear to be similar to that of accelerated hypertension unassociated with pregnancy. If the other maternal manifestations of pre-eclampsia have a similar pathogenesis to proteinuria then these also are a direct result of hypertension. A common pathogenesis is

Table 1. Comparison of characteristics at entry to trial

	Test group ($n = 17$)	Control group ($n = 19$)
Age (years)	33·5 (6·6)	30·5 (6·3)
Parity		
Nulliparae	5 (29%)	7 (37%)
Multiparae	12 (71%)	12 (63%)
Blood pressure (mmHg)*		
Systolic	167 (15)	162 (11)
Diastolic	104 (9)	101 (9)
Hypertension		
Pregnancy-induced	12 (71%)	13 (68%)
Pregnancy-associated	5 (29%)	6 (32%)

* Blood pressure = mean of two measurements made on two separate days.

Results are means (SD) or *n* (%) as appropriate

Table 2. Response of blood pressure to treatment

	Test group ($n = 17$)	Control group ($n = 19$)
	Mean (SD)	Mean (SD)
Blood pressure (mmHg)		
Initial		
Systolic	167 (15)	162 (11)
Diastolic	104 (9)	101 (9)
Highest during treatment		
Systolic	142 (16)	164 (15)
Diastolic	91 (10)	102 (10)
Before onset of labour or at onset of proteinuria		
Systolic	130 (19)	157 (15)
Diastolic	85 (10)	101 (8)

Table 3. Analysis of results

	Test group (n = 17)	Control group (n = 19)	Significance level
Proteinuria	1 (6%)	6 (32%)	$P = 0·05$
Median Apgar score			
At 1 min	9	9	NS
At 5 min	9	9	NS
Gestational age at delivery (weeks)	37·0 (2·6)	38·3 (1·8)	NS
Bithweight (g)	2508 (922)	3163 (980)	$P<0·05$
Birthweight centile*			
>50th	2 (12%)	9 (47%)	$P<0·05$
<50th	15 (88%)	10 (53%)	
Perinatal deaths	2 (12%)	1 (5%)	NS

* According to Hayes *et al.* (1983)

Results are means (SD) or n (%) as appropriate.

strongly supported by the similarity with the complications of accelerated hypertension, and practical experience would also lend support in that the extra-renal manifestations of pre-eclampsia rarely if ever occur without proteinuria. Hence, it is common practice to use proteinuria as a marker for pre-eclampsia.

This hypothesis presupposes that pre-eclampsia does not occur in the absence of hypertension. Experience would suggest that this is so. It is noteworthy that the risk of pre-eclampsia increases with the severity of the hypertension (Mabie *et al.* 1986). While the blood pressure level in pre-eclampsia may occasionally appear to be within the normal range, as judged by levels in the non-pregnant state, it is known that complications of hypertension, such as hypertensive encephalopathy, depend more on the rate of increase of blood pressure than the absolute size of the increase. A rapid rise from normal to as little as 150/100 mmHg has been known to cause encephalopathy (Kaplan 1980).

It would appear then that the control of hypertension to the normal level for pregnancy would prevent the clinical maternal manifestations of pre-eclampsia It may not necessarily prevent subclinical maternal changes of a histological nature affecting tissues such as the endometrium. For instance, it is known that retrograde vascular infiltration by trophoblast occurs before 19 weeks gestation (Robertson 1976), so that the defective infiltration typical of pre-eclampsia anticipates clinical pre-eclampsia by some weeks. It may be that such subtle abnormalities are the earliest changes in hypertensive pregnancy and that they could be avoided only by anticipating and preventing the development of hypertension. Alternatively it is quite possible that these represent the initial abnormalities which lead on to hypertension which in turn causes the maternal manifestations. However, this study is concerned only with those maternal manifestations of pre-eclampsia which present clinically.

There were three perinatal deaths, two in the test group and one in the control. This difference is not significant for the numbers involved in this study, but was of sufficient concern to the ethics committee to advise cessation of the study. Given the relative rarity of perinatal deaths in general, it would require a very much larger, possibly multicentre study to establish a link between the treatment regimen and perinatal mortality (Thorley *et al.* 1981).

Intensive hypotensive treatment in the test group did appear to have an adverse effect on fetal development. When birthweight was adjusted for gestational age, a significantly higher percentage of babies in the test group was underweight. It follows that what benefits the mother may not benefit the fetus. A consideration of placental anatomy and haemodynamics may cast further light on this. The destruction of the endometrial arterioles by trophoblast removes the main component of the peripheral resistance, and at the same time the disruption of the muscular walls of the greater portion of the spiral arteries converts them into dilated, non-contractile channels making placental blood flow critically dependent on the head of pressure in the uterine arteries (Robertson 1976). Since placental blood flow is already compromised in pre-eclampsia in spite of an elevated perfusion pressure, the immediate effect of blood pressure reduction may be a further reduction in fetal blood supply. Much depends on whether or not blood flow autoregulation exists in the placental circulation. It is unlikely since autoregulation is an arteriolar function.

It would appear from the results of the present study that while reduction of pregnancy hypertension to near normal for the stage of pregnancy will protect the mother from the clinical manifestation of pre-eclampsia, such a policy cannot be confidently recommended for the welfare of the fetus. In the light of present knowledge the only safe recommendation is that hypertension be treated to the degree considered necessary to protect the mother from serious damage.

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A case-control study of the effects of birth by caesarean section on intrapartum and neonatal mortality among twins weighing 1500–2499 g

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Summary. The aim of this nationally-based, matched case-control study was to assess the impact of birth by caesarean section on intrapartum, and neonatal mortality among twins weighing 1500–2499 g, born in Sweden between 1973 and 1983. By using data held at the National Medical Birth Registry, Stockholm, 91 such pregnancies (study cases) where one or both twins died were identified. For each case, two controls (in all 182 pregnancies) were allotted at random from the rest of the twin pregnancies, with similar birthweight (±100 g) and year of delivery (±1 year). The number of twins that died was reduced from 73 during the first four years to 22 between 1977 and 1980, and to 6 during the last 3 years of the study period. Almost a quarter (23.1%) had a lethal malformation. The caesarean section rate increased during the study period, but did not differ between cases and controls ($\chi^2 = 1{\cdot}0$; $P{>}0{\cdot}05$). The analysis could not confirm a significant difference between cases and controls regarding the number of infants born vaginally in non-vertex presentation ($\chi^2 = 0{\cdot}1$; $P{>}0{\cdot}05$). The results of this study appear to indicate that birth by caesarean section was not a major factor related to the improved fetal outcome.

Twins have a perinatal mortality 4–6 times as high as singletons (Hoffman & Bakketeig 1984), the increased frequency of preterm delivery and immature newborns being the main causes (Ho & Wu 1975). The preterm twin also runs an increased risk of malpresentation leading to birth trauma and fetal asphyxia (Bell *et al.* 1986; Taylor 1983, Ware 1971). Other complications during labour include twin interlocking, cord prolapse and placental abruption (Trofatter 1988).

To improve the fetal prognosis, caesarean section has been proposed for twins with presentations other than vertex-vertex, and particularly when gestational age is less than 34 weeks (Cetrulo 1986; Chervenak & Chervenak 1988). Such a policy has been reported to result in caesarean section being preferred in more than 80% of deliveries at 34 weeks or less, and more than 60% at 35 weeks or more (Cetrulo 1986). In pregnancies with the twins in vertex-vertex presentation, reports have shown favourable fetal outcome after vaginal delivery, irrespective of the birthweight of the twins (Chervenak & Chervenak 1988). However, most studies have analysed hospital populations

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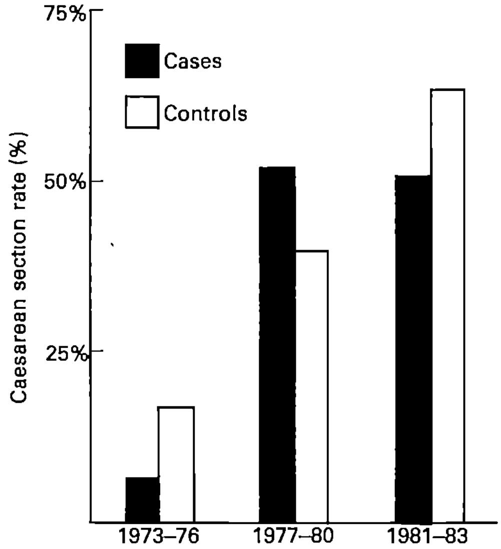

Fig. 1. Caesarean section rate for cases (pregnancies with one or both twins dead) and controls (pregnancies with both twins surviving).

and small numbers (Effer *et al.* 1983; MacGillivray 1988).

The present study was undertaken in order to test the rationale of the above-mentioned policy. To improve the power of the study, an analysis was based on all twin deliveries in Sweden and was designated as a matched case-control study. The impact of caesarean birth on intrapartum and neonatal mortality for twins weighing 1500–2499 g born in Sweden between 1973 and 1983 was assessed.

Subjects and methods

The National Medical Birth Registry, at the National Board of Health and Welfare, Stockholm, was used to identify all 6608 twins with a birthweight between 1500 and 2499 g (twin pregnancies with fetal death before labour were excluded), born in Sweden between 1973 and 1983. Of these, 104 twins (91 pregnancies) died during labour or within 28 days after birth. According to the official statistics, 9574 twin deliveries (all birthweights included) occurred between 1973 and 1983; 231 of these pregnancies (2·4%) were not on record at the Medical Birth Registry (Population Changes 1974–84).

For each study case, two controls (pregnancies with both twins surviving the neonatal period) were chosen, thus creating 'triads' for analyses. For this purpose Sweden was divided into five regions, and for each case, two controls were selected at random from among eligible pregnancies in the same region. The controls were matched for mean birthweight in the pair (±100 g). and for year of delivery (±1 year).

The original medical records for cases and controls were retrieved for assessment of gestational and neonatal factors influencing morbidity and mortality, and the autopsy reports were reviewed.

To assess whether the study cases and their controls had significantly different caesarean section rates, McNemar's test for significance of change was used (Miettinen 1969). This analysis excludes non-informative 'triplets' (one case, two controls) where the case as well as the two control pregnancies had been delivered vaginally, or abdominally. When labour was present at the time of decision to deliver abdominally, the procedure was classified as an emergency one.

The non-vertex position as a risk factor was analysed in a similar way using McNemar's test. In order to study this problem restricted to vaginal or abdominal deliveries, the matching was broken and instead the analysis was based on the Mantel-Haenszel technique (Mantel & Haenszel 1959) after stratification for year of delivery (1973–76, 1977–80, 1981–83) and birthweight (1500–1999 g, 2000–2499 g). The odds ratio (OR) with 95% confidence intervals (CI) was estimated for cases in a non-vertex presen-

Table 1. Total number of twins with a birthweight between 1500 g and 2499 g and mortality (intrapartum and neonatal) for 104 twins (91 pregnancies) in the three study periods (twin pregnancies with fetal death before labour are excluded)

	1973–76	1977–80	1981–83	Total
Total no twins	2543	2322	1743	6608
Twin I (*n*)	13	8	2	23
Twin II (*n*)	38	13	4	55
Both twins dead (*n*)	22	4	–	26
Total no. of dead twins	73	25	6	104
Mortality (%)	2·9	1·1	0·3	1·6

Table 2. The main indication for abdominal delivery for cases (one or both twins dead intrapartum or neonatally) and for controls (both twins surviving the neonatal period)

	Cases (n)	Controls (n)
Preterm including breech presentation	2	12
Haemorrhage, including placental abruption	6	7
Tranverse lie, risk for twin interlocking	3	9
Impending asphyxia, including umbilical cord prolapse	5	3
Contracted pelvis, dystocia	–	6
Abdominal delivery of twin II	–	3
Malformed twin*, PROM*, bad obstetric history*	3	2
Pre-eclampsia*	–	3
Acute pancreatitis*, discordant birthweight*	–	2
Total	19	47

*Caesarean section electively performed.
PROM = prelabour rupture of membranes.

tation, compared with controls (Miettinen 1974). A significant rise in the odds ratio indicates an increased rate of twins in non-vertex presentation in cases compared with controls. To test for heterogeneity, the χ^2-analysis with one degree of freedom (df) was used. Student's t-test was applied to compare the birthweights of cases and controls. A P-value of <0·05 was considered significant.

Results

The section rate increased (Fig. 1) for both cases and controls, from under 20% in the first period (1973–76) to 50–65% in the last period (1981–83). Concomitantly, the number of dead twins per period decreased, from 73 to 6 (Table 1). On applying McNemar's test to the numbers of sections, no significant difference was evident between cases and controls (χ^2 = 1·0; OR = 0·7; 95% CI 0·1 to 1·4). When caesarean section was studied as a risk factor within triads with a known presentation of both twins (n = 81), an odds ratio of 0·7 was found (χ^2 = 1·0; 95% CI 0·4–1·4). After exclusion of twins with lethal malformations, the odds ratio was 1·4 (n = 63; χ^2 = 0·7; 95% CI 0·6–3·3). For the first three years of the study period (1973–75, n = 38) the odds ratio was 2·1 (χ^2 = 0·9; 95% CI 0·4 to 10·5) and for the last 8 years (1976–83, n = 25) it was 1·2 (χ^2 = 0·1; 95% CI 0·4 to 3·3). The main indications for abdominal delivery are given in Table 2. A similar, low rate of elective section (≤15%) was seen for cases and controls.

Mode of delivery related to different presentations is shown in Table 3. When fetal presentation was analysed as a risk factor, the odds ratio for non-vertex presentation was 1·3, (χ^2 = 0·9; 95% CI 0·8 to 2·1) and when lethal malformations were excluded, 1·2 (χ^2 = 0·5; 95% CI 0·7 to 2·2). After breaking the matching, an analysis based on the Mantel-Haenszel method was made of fetal presentation as a risk factor related to different delivery methods. For vaginal deliveries, the odds ratio was 1·2 (χ^2 = 0·1; 95% CI 0·5 to 2·7) and for abdominal deliveries it was 0·8 (χ^2 = 0·0; 95% CI 0·1 to 12·4).

Table 4 shows the causes of death; the autopsy rate was 82%. It is notable that nearly a quarter of the dead twins (23·1%) had (potentially) lethal malformations such as cardiac defects or anencephaly (Table 5). The most common cause of death was immaturity, including asphyxia (48·1%), and in this group a difficult extraction was more common among second twins than for first twins. The mortality rate (13 pregnancies with both twins dead excluded) was significantly higher for twin II than for twin I (χ^2 = 26·3; P<0·001).

The number of operative vaginal deliveries for the second twin, including abdominal delivery of the second twin after vaginal delivery of the first twin, did not differ (χ^2 = 0·8; P<0·05) between cases (n = 15) and controls (n = 23). Podalic internal version and extraction for the second twin was done in 12 cases and 14 controls, a difference which is not statistically significant (χ^2 = 2·3; P>0·05). The birthweights for cases and controls were similar for first twins (2045 g *vs* 2002 g; t = 0·8; P>0·05) and for second twins (1913 g *vs* 1973 g; t = 1·4; P>0·05). When cases with one dead twin were analysed, twin I and twin II had similar birthweights (1937 g *vs*

Table 3. Presentation at delivery and the corresponding caesarean section (CS) rate for cases and controls

Presentation	Cases Total *n* (%)	Cases CS (%)	Controls Total *n* (%)	Controls CS (%)
Vertex-vertex	38 (41·7)	7·9	91 (50·0)	16·4*
Vertex-breech	26 (28·6)	7·8	44 (24·2)	22·5*
Breech-vertex	10 (11·0)	40·0*	21 (11·5)	47·6
Breech-breech	13 (14·3)	54·0	19 (10·4)	36·8
Not known	4 (4·4)	25·0	7 (3·8)	14·3
Total	91 (100·0)	18·7	182 (100·0)	23·6

*Including pregnancies with abdominal delivery of the second twin after vaginal delivery of the first twin.

Table 5. Congenital malformations found in 23 twins dying during labour, or neonatally

	No. twins
Cardiac defects, including elastosis	7
Atresia in the gastro-intestinal tract, and defects in the diaphram and abdominal wall	6
Urinary system defects, including Potter's syndrome	5
Acrany/anencephaly	4
Trisomy 13	1

1870 g; $t = 1{\cdot}0$; $P{>}0{\cdot}05$). A similar length of gestational was seen for cases and controls and the mean difference (each case *vs* mean of its two controls) was 2 days±2 days (m±SEM).

Discussion

The National Medical Birth Registry has collected data on all deliveries in Sweden since 1973. This database allowed us to identify a large number of cases where one or both twins had a birthweight between 1500 and 2499 g. Information on length of gestation is not entirely valid in the Medical Birth Registry. This is why control gestations were matched for birthweight (and year of delivery). However, after retrieval of the original medical records it was found that a similar gestational duration was present in cases and controls.

During the 11-year period studied, the caesarean section rate increased considerably and in like manner for cases and controls. Concomitantly the number of dead twins decreased, from 73 during the first 4 years of the study period to six during the last 3 years. However, abdominal delivery did not emerge as being protective against death. The interpretation is complicated by the fact that when caesarean section is carried out because of a life-threatening condition for the fetus (such as placental abruption) the caesarean section would then appear as a risk factor. When the first 3 years of the study were compared with the remaining years, there were indications that the odds ratio was higher during the former than during the latter period, but despite the fact that the analysis is based on a large dataset, this difference may be due to chance. It could indicate, however, that the increasing use of caesarean section during the period actually resulted in a reduced death risk. The estimated odds ratio could contain two counteractive components: one the above mentioned confounding effect of life-threatening conditions, the other a beneficial effect of caesarean section on fetal mortality.

An increased perinatal mortality for low birthweight twins born vaginallly in non-vertex presentation has been reported (Ware 1971; Taylor 1983; Cetrulo 1986; Chervenak & Chervenak 1988). In the present study non-vertex presentation was not seen significantly more often

Table 4. Causes of death related to twin I or twin II and mode of delivery

Cause of death* No. of twins	Twin I 36	Twin II 68	Vaginal delivery 85	Abdominal delivery 19	Total 104
Immaturity and/or asphyxia†	15	35	40	10	50
difficult extraction	1	9	7	3	10
Congenital malformation	11	13	19	5	24
Other diagnoses	1	9	8	2	10
Neonatal infection	–	5	5	–	5
Obscure	8	17	20	5	25

*In some instances more than one diagnosis for each twin was applied.

†Including one case of twin interlocking, one case of placental abruption and one case of cord prolapse.

among cases then among controls, indicating that such a presentation *per se* is not a major factor related to the poor fetal outcome for twins weighing 1500–2499 g.

Second twins had a consistently higher intrapartum and neonatal mortality than first twins, irrespective of study period or caesarean section rate. No significant difference was found in the birthweight between the two groups of twins. The proportions of operative vaginal delivery and abdominal delivery of the second twin after vaginal delivery of the first twin were also similar for cases and controls. Severe intrapartum complications such as twin interlocking, cord prolapse, and placental abruption leading to death were rarely recorded (3 cases). Accordingly, the present study offers no explanation for the significantly worse prognosis for the second twin. A matched case-control study in twin pregnancies has reported previously a higher rate of idiopathic respiratory distress syndrome among second twins (Arnold *et al.* 1987), a finding that was not analysed in the present study.

The considerable reduction in the number of dead low birthweight twins during the 11-year study period seems likely to be due to a number of factors. The benefits of fetal monitoring, and ultarsound scanning to identify fetal position even before delivery of the first twin were not analysed separately in the present study, but may have played a significant role. The regionalization of perinatal care and improvements in the care of the newborn are other factors that might be responsible for the reduction in mortality in twin pregnancies.

It should be noted that a quarter of the twins that succumbed died of severe and potentially lethal malformations. These findings indicate that twin pregnancies in preterm labour should be investigated sonographically to identify twins with severe malformations. Such a diagnosis might lead to a decision to refrain from caesarean section.

In conclusion, intrapartum and neonatal mortality among low birthweight twins (1500–2499 g) was higher among second twins and babies with congenital malformations, but not higher among babies born vaginally or among those who had a non-vertex presentation.

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Women who gain more fat during pregnancy may not have bigger babies: implications for recommended weight gain during pregnancy

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Summary. The correlation between infant birthweight and the amount of fat gained during pregnancy (estimated as the change in maternal weight between 10 weeks gestation and 2–3 weeks postpartum) was studied in 115 healthy, parous, urban Scottish housewives. There was very little correlation between these variables ($r = 0{\cdot}13$, falling to $r = 0{\cdot}07$ after birthweight was adjusted for initial maternal weight and length of gestation), i.e., women who gained more fat during their pregnancies did not give birth to heavier babies. This suggests that for most women one of the principal effects of increasing food intake during pregnancy may be to increase maternal fat gain rather than promote fetal growth, and that efforts to increase birthweight by encouraging greater weight gain during pregnancy may be unsuccessful.

Two important studies published in the late 1960s established a weak positive correlation between maternal weight gain and birthweight and showed that women who gain little weight during pregnancy have an increased risk of low birthweight babies (Singer *et al.* 1968; Eastman & Jackson 1968). Before 1970 it was common practice in the United States to restrict maternal weight gain to about 10 kg (Singer *et al.* 1968; Eastman & Jackson 1968; Niswander & Jackson 1974; Simpson *et al.* 1975), compared with an average gain in the UK of about 12·5 kg (Hytten 1980). This lower weight gain seemed to offer a potential explanation for the lower average birthweight among US women at the time and higher recommendations for maternal weight gain followed. In 1970 the National Academy of Sciences Committee on Maternal Nutrition and the Course of Pregnancy recommended that 'the desirable average gain is 24 lb (10·9 kg) within a range of 20–25 pounds (9–11·5 kg) (NRC 1970) This has since been interpreted to indicate that all women should gain at least 11 kg (Abrams & Laros 1986, Frentzen *et al.* 1988), and two large recent surveys in the US reported average maternal weight gains of about 15 kg (Abrams & Laros 1986; Shepard *et al.* 1986). In addition, one recent expert panel has suggested that 15 kg represents the desirable average gain for women of average initial body weight (Brown *et al.* 1990). By European standards a weight gain of 15 kg is relatively high (Hytten 1980; Durnin *et al.* 1987), which indicates that the pendulum, in terms of dietary advice to pregnant women, has swung too far in the US with the result that excessive weight gain is being encouraged in a considerable number of women. The average figure of 12·5 kg generally accepted for the UK already includes an allowance of 3·5 kg for adipose tissue, and this is likely to increase as weight gain increases. The data of both Billewicz & Thomson (1970) and Greene *et al.* (1988) suggest that high rates of weight gain during preg-

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nancy lead, in some women, to the retention of undesirable amounts of weight post-partum, and our own data support this (Lawrence *et al.* 1988). Clearly, the potential benefits to the fetus of a high rate of weight gain must be balanced against the risks for the mother of encouraging the development of unwanted fatness.

The general interpretation of the positive relation between maternal weight gain and birthweight is that there is a causal link between maternal energy intake, weight gain during pregnancy and birthweight (Rush *et al.* 1972; Lechtig *et al.* 1975; Jacobson 1977; Rosso 1985, Winick 1986, Brown *et al.* 1990). The problem is that maternal weight gain includes the weight of the baby and a positive correlation with birthweight is therefore inevitable. This problem is compounded by the fact that maternal weight gain also includes the placenta and amniotic fluid, plus increases in uterine mass, blood and tissue fluid, the weights of which are also correlated with fetal weight (for reasons that may have very little to do with the level of energy intake). These added tissues and fluids plus the weight of the baby account for about 70% of total weight gain (Hytten 1980). In view of this it is perhaps surprising that the correlation between maternal weight gain and birthweight is reported to be no stronger than between 0·2 and 0·3 (Niswander & Gordon 1972; Niswander & Jackson 1974; Simpson, Lawless & Mitchell 1975; Rantakallio *et al.* 1981; Anderson *et al.* 1984; Abrams & Laros 1986). The pertinent question would appear to be whether there is a correlation between birthweight and maternal fat gain since the woman who increases her energy intake by more than average during pregnancy might not only be expected to give birth to a heavier baby but also to gain more fat. In a series of 56 women, Langhoff-Roos *et al.* (1987) found little correlation between maternal fat accretion and birthweight, but, as they pointed out, their estimates of fat gain were relatively imprecise.

In a separate study in 64 women we obtained daily measurements of body weight before delivery and for the first 28 days post-partum (Lawrence *et al.*). Mean weight loss on the day of delivery was 5·6 kg (SD 1·4 kg) and by the end of the second week it was 8·9 kg (SD 1·9 kg), with the most rapid loss occurring between 4 and 10 days post-partum. These losses are consistent with the uterus being resorbed and most of the additional blood and fluid gained during pregnancy being lost by 14 days post-partum. The rapid weight loss between 4 and 10 days post-partum (2·4 kg) can only have been fluid, and the total amount of weight loss by 14 days (8·9 kg) was very similar to the combined weight of the fetus, placenta, uterus, blood and fluid as estimated by Hytten (1980), i.e., 8·75 kg. In the third and fourth weeks weight loss was much more gradual (about 0·25 kg/week), consistent with a gradual mobilization of adispose tissue. Assuming little adipose tissue was also lost in the first 2 weeks post-partum, we suggest that the amount of fat gained during pregnancy can reasonably be estimated from the increase in maternal weight between early pregnancy and 2–3 weeks post-partum (Lawrence *et al.* 1988). This additional weight will consist of adipose tissue gained during pregnancy plus any increase in breast tissue (presumably a minor and relatively constant component). In this paper we report the correlation between this simple measure of maternal fat gain and birthweight in a preliminary study of 115 Scottish women.

Subjects and methods

The 115 women studied were urban housewives from Glasgow and the surrounding area who responded to calls for healthy pre-pregnant and early pregnant volunteers to take part in longitudinal studies of the energy requirements of pregnancy (Durnin *et al.* 1987). They were drawn from a variety of social groups within the city, and were selected on the basis of age (20–35 years), parity (they should already have had one full-term live-born infant) and an intention to breast-feed (at 2 months post-partum, 79% of women were either partially or exclusively breast-feeding). No attempt was made by the women's physicians to restrict weight gain during pregnancy. Only women who did not smoke, who had uncomplicated pregnancies and who gave birth to live singleton infants at term ($\geq$37 weeks gestation) were included in the present analyses. Because of these selection criteria data from eight women were excluded.

Body weight, in light clothing, was measured immediately before or as near conception as possible and then at regular intervals throughout pregnancy and for at least the first 2 months post-partum. The maximum interval between measurements was 6 weeks, but sub-samples of women were measured more frequently, at intervals of 2 and 4 weeks. Differences in measurement frequency arose because the main project (dealing with the energy requirements of pregnancy) was carried out in three phases, and there was therefore no relation between the frequency of measurement and any of the maternal characteristics of interest (e.g., the amount of weight gained). In addition to body weight, four skinfold thicknesses (biceps, triceps, sub-scapular and supra-iliac) were measured and were used to calculate body fat content early in pregnancy and in the post-partum period, using the equations of Durnin & Womersley (1974). Body fat content in mid- and late-pregnancy was not calculated because suitable equations are not available for these times. Data collected at four stages during pregnancy and lactation were used in the present analyses. These stages were (i) 7–13 weeks gestation (mid-point 10 weeks), (ii) 21–27 weeks (mid-point 24 weeks), (iii) >34 weeks (mid-point 38 weeks) and (iv) 2–3 weeks post-partum (mid-point 2·5 weeks). For each subject, all available data for each time period were averaged, and differences in body weight and skinfold thicknesses between the various stages were calculated. In 30 of the 115 women the initial post-partum measurement was not made until 4–7 (average 5·5) weeks post-partum. In these women, body weight 2·5 weeks post-partum was estimated from the weight at 4–7 weeks after delivery assuming a uniform rate of loss of 0·25 kg/week (ie the average over this period for the group as a whole).

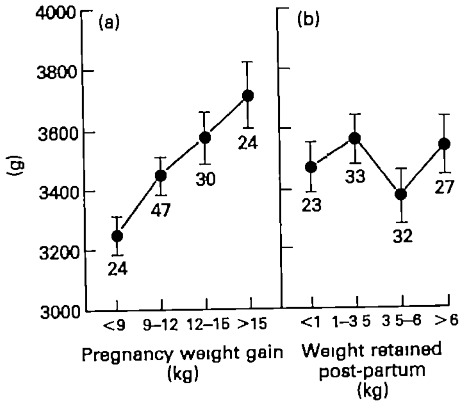

Fig. 1. Birthweight of Scottish infants, adjusted for initial maternal weight and length of gestation, according to (a) pregnancy weight gain and (b) retained weight gain. The mean, standard error and number of subjects are given

Results

Linear regression analysis was used to establish the correlation between birthweight and maternal weight gain, and multiple linear regression analysis was used to repeat the analysis but after adjusting birthweight for the initial maternal weight and length of gestation. There was, as expected, a positive correlation between maternal weight gain and either birthweight (r = 0·47) or adjusted birthweight (r = 0·39, $P<0{\cdot}001$), but there was very little correlation between retained maternal weight gain (estimated as the change in maternal weight between 10 weeks gestation and 2–3 weeks post partum) and either birthweight (r = 0·13) or adjusted birthweight (r = 0·07, $P>0{\cdot}05$). These data are presented in Fig. 1. Other characteristics of the four groups compared in Fig. 1b are given in Table 1. There were no significant differences between the groups in height, initial fatness of the mother or length of gestation. Nor were there any differences in maternal age, parity or sex of offspring (not shown). There were, however, significant differences in weight at 10 weeks gestation ($P<0{\cdot}01$), but these had little effect on the correlation between birthweight and retained weight The groups also differed in terms of weight gain during pregnancy and in the changes during pregnancy in skinfold thicknesses (Fig. 2). In women with a retained weight gain of <1 kg, the total weight gain during pregnancy was 8·2 kg (an average of about 0·29 kg/week between 10 and 38 weeks), whereas those women with a retained weight gain of >6 kg, gained on average 16·5 kg (about 0·6 kg/week). Within each group similar amounts of weight were gained in the second and third trimesters, but the amount of fat gained differed markedly between trimesters (Fig. 2). In the women retaining least weight the sum of three skinfold thicknesses (biceps, triceps plus sub-scapular) increased slightly during the second trimester ($P<0{\cdot}05$), but fell again during the third trimester to levels not significantly different from those measured initially, whereas in women retaining the most weight, skinfold thicknesses increased steadily throughout pregnancy (Fig. 2). (Supra-iliac skinfold thickness was excluded from these analyses because of the difficulty of measuring this skinfold accurately near term.)

Discussion

Given that most of the weight retained beyond

Table 1. Initial maternal characteristics at 10 weeks gestation and pregnancy outcome in Scottish women by amount of fat gained during the pregnancy (estimated as change in weight between 10 weeks gestation and 2–3 weeks post-partum)

	Post-partum weight retention (kg)				
Variable	<1 (*n* = 23)	1–3·5 (*n* = 33)	3·5–6 (*n* = 32)	>6 (*n* = 27)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F-ratio*
Height (mm)	1608 (63)	1625 (70)	1619 (48)	1630 (78)	0·5
Initial weight (kg)	59·0 (8·8)	54·7 (6·7)	56·4 (5·2)	61·0 (7·2)	4·6†
Initial % fat	26·3 (3·5)	23·6 (4·9)	25·2 (3·5)	26·0 (4·5)	2·5
Length of gestation (weeks)	39·7 (1·1)	39·7 (1·1)	39·9 (1·4)	40·1 (1·1)	0·8
Weight gain between 10 and 38 weeks (kg)	8·2 (2·6)	10·4 (1·8)	12·3 (2·1)	16·5 (2·9)	58·9**
Weight retained post-partum (kg)	−0·6 (1·4)	2·3 (0·8)	4·8 (0·7)	8·6 (2·4)	187**
Birthweight (g)	3485 (466)	3486 (424)	3360 (580)	3641 (546)	1·5
Adjusted birthweight (g)‡	3468 (404)	3557 (440)	3370 (501)	3537 (521)	1·0

* F-ratio for statistical significance of difference between groups by analysis of variance (3 and 111 degrees of freedom), † $P<0{\cdot}01$, ** $P<0{\cdot}001$.

‡ adjusted for initial maternal weight and length of gestation.

about 2 weeks post partum is likely to be adipose tissue, the virtual absence of a correlation between birthweight and retained weight could have considerable physiological importance. Our results suggest that over quite a wide range (retained weight varied from −3 kg to +14 kg), the fetus may be relatively protected against the potentially adverse effects of maternal energy imbalances, and may obtain the nourishment it needs irrespective of maternal fat gain or loss. The implication is that either increasing or decreasing maternal energy intake during pregnancy may have little impact on birthweight, but could have quite a marked effect on materanl fat accretion. This runs counter to much advice currently given to pregnant women, which is that increasing energy intake will increase both weight gain during pregnancy *and* birthweight (Rush *et al.* 1972, Lechtig *et al.* 1975; Jacobsen 1977; Rosso 1985; Winick 1986; Brown *et al.* 1990), with a consequent decline in the risks attached to low birthweight babies.

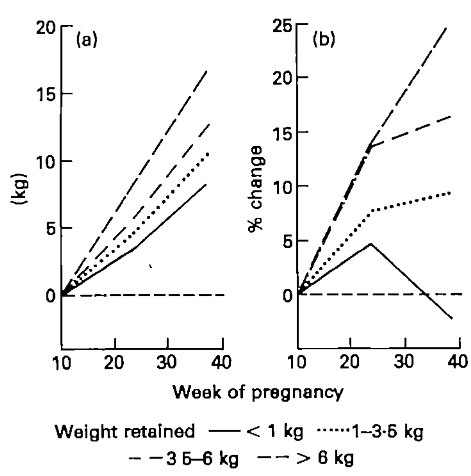

Fig. 2. (a) Maternal weight gain and (b) % changes in the sum of three skinfold thicknesses in groups of women retaining different amounts of weight post-partum.

A potential criticism of the current study relates to the relatively small sample size, and the fact that a difference in birthweight between low and high weight-retainers may not have been detected because insufficient numbers of women were included in these groups. Power tests indicate that with the current study design and with a sample size of 100 there would have been a 90% chance of detecting an increase in birthweight of 50 g for each additional kg of weight retained, but a lesser chance of detecting a smaller increase in birthweight. Potentially, an increase in birthweight of less than 50 g/kg weight retained could still be physiologically important. Suppose, for example, there was a 25 g increase in birthweight for each additional kg of weight retained, then in this study the group of high weight-retainers might have been expected to give birth to babies weighing on average 230 g more than the group of low weight-retainers (for a difference in weight retention between the groups of 9 kg). Depending upon the circumstances (e.g., average birthweight of the group as a whole, frequency of low birthweight, etc.) such a difference in birthweight could well be important, and to that extent the criticism that the present sample size is too small is justified. However, even if there were a positive correlation between maternal fat gain and birthweight that went undetected in the present study, it would appear that quite substantial increases in maternal fat gain would be needed before there was any marked effect on birthweight.

There are also other reasons for caution in interpreting the results reported here. There may, for example, be a threshold for maternal fat gain below which fetal growth is compromised, but above which fluctuations in maternal energy balance may have little effect (Stein & Susser 1975; Prentice *et al.* 1983; Viegas *et al.* 1982). If this is the case, our results indicate that quite substantial amounts of fat may have to be lost before this threshold is crossed, since the group of low weight-retainers we studied lost 0·6 kg between 10 weeks gestation and 2–3 weeks post-partum, but nonetheless had babies of quite satisfactory birthweight. In this group average weight gain during pregnancy was only about 8 kg. A second factor is that the women we studied were in general of average body weight and body fatness initially, and it is possible that in women who begin pregnancy with a reduced body weight or depleted maternal fat stores, an increase in fat content during pregnancy may be of greater physiological importance. It has, for example, been suggested that the slope of the line relating birthweight to weight gain is steeper in initialy under-weight women (Niswander & Gordon 1972, Brown *et al.* 1981; Rosso 1985), which may indicate that in these women there is indeed a positive correlation between birthweight and fat gain. However, further studies of the composition of weight gained during pregnancy by underweight women are needed to confirm this since there are other potential explanations for a steeper slope, such as less variable maternal fat gain or relatively greater fluid gain.

In conclusion, the results of the current study indicate that in women of initially average body weight and fatness there may not be a direct causative link between maternal energy intake, weight gain during pregnancy, and birthweight. Women who presumably increase their energy intake by more than average during pregnancy, and who in consequence gain considerable amounts of fat, nonetheless give birth to babies who are no heavier than those born to women losing some fat overall. It seems unlikely, therefore, that efforts to increase birthweight by encouraging greater weight gain will achieve the desired result, at least in women of initially average body weight, and may only have the effect of increasing the amount of fat gained by the mother. The position is less clear in women who are underweight initially and in those with pregnancy weight gains of <5 kg (i.e., the minimum observed in the current study, and corresponding to a loss of about 3 kg of weight between early pregnancy and 2–3 weeks post-partum). In both these groups some additional increase in energy intake may be of benefit potentially, and can be advised. At the other end of the spectrum, however, women gaining large amounts of weight during pregnancy (>0·6 kg/week or >16 kg overall) are more likely to retain undesirable amounts of fat post-partum (Lawrence *et al.* 1988), and these women could be counselled to reduce their energy intake somewhat so as to bring their weight gain down towards a more average figure of about 0·4 kg/week. Clearly, we do not advocate a strict programme of weight control for all women (as practised by US physicians in the 1960s), nor do we suggest that very low energy intakes during pregnancy are in any way desirable. The modest reductions in energy intake we would advocate for some women are most unlikely to have any adverse effect on birthweight but may combat the problem of excessive fat gain by the woman.

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Stopping smoking in pregnancy: effect of a self-help manual in controlled trial

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Summary. For medical reasons, encouraging women to stop smoking during pregnancy and post partum has high priority. Many smokers want to stop smoking but decline clinical treatment when it is offered. The aim of this study was to find a method which was accepted by a large number of smokers, had a high success rate and, at the same time, required little involvement from personnel. For one year, all pregnant smokers attending 13 of the 14 public health maternity clinics in Gothenburg for their first appointment were invited to participate in this study. Inclusion criteria were daily smoking, a gestational age of less than 12 weeks and ability to understand Swedish. A total of 745 women was registered, but 22 of them stopped smoking before the treatment. The remaining women were randomized to a treatment group (*n* = 492) and a control group (*n* = 231). Of the 492 women in the treatment group 417 (85%) accepted the idea of using the self-help manual written especially for pregnant women and given to each woman in the treatment group by the obstetrician. Overall 10·4% of the treatment group stopped smoking up to 8 weeks after delivery compared with 5·2% of the control group (odds ratio 0·5, 95% CI 0·2–0·9). The ex-smoking status was verified by measurement of thiocyanate in blood. The self-help manual had a high acceptance rate and a success rate that was double the rate in the control group.

There is now a general agreement that smoking in pregnancy negatively affects intrauterine growth in a dose dependent manner. Recently this growth retardation was shown to result in a significant increase in fetal morbidity and mortality. Cnattingius *et al.* (1988) found that the relative risk of intrauterine death was 1·4 and for early neonatal death 1·2, if the mother was a smoker. Other negative effects of maternal smoking include an increased rate of miscarriage (Johnston 1981).

About 30% of the pregnant women in Sweden are smokers (Cnattingius *et al.* 1988). It seems as if the health consequences of smoking either are not known or ignored, as only 20% of smokers quit when they know they are pregnant (Cnattingius 1989). This proportion is the same in Sweden as in Great Britain and the United States (Ashford *et al.* 1986; Macarthur *et al.* 1987; Sexton & Hebel 1984).

Strong motivation to stop smoking is a crucial factor. For those who continue to smoke, pregnancy is obviously not a strong enough reason, and most of them will go on smoking for the rest

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of their pregnancy. Judging from results based on control groups in randomized trials, fewer than 6% stop smoking spontaneously later in pregnancy (Macarthur *et al.* 1987; Sexton & Hebel 1984; Baric *et al.* 1976; Ershoff *et al.* 1983; Windsor *et al.* 1985).

In a general population interventions to stop smoking, based on facts about health hazards of smoking and advice on how to stop, have been assessed. Leaflets, self-help manuals, posters, TV programmes and minimal interventions from doctors resulted in 2–5% stopping smoking (Davis *et al* 1984; Li *et al.* 1984). Only a few published studies have followed-up the effect of interventions to stop smoking in pregnancy. Macarthur *et al.* (1987) distributed leaflets to pregnant women and found that 9% were able to stop smoking compared with 6% in a control group. The amount of smoking in the two study groups was not validated chemically so the effect may have been overestimated. A self-help manual written especially for pregnant women resulted in 14% stopping smoking compared with 6% for a self-help manual directed to men and women generally (Windsor 1985).

Still more successful but also more time and personnel-consuming methods have been reported. Ershoff *et al.* (1983) used a home correspondence programme. Half of the women who received it abstained from smoking during pregnancy, included in this group are those who quit on their own whey they became pregnant. Sexton & Hebel (1984) used programmes where the smokers received new home assignments every week, supplemented with home visits and telephone calls. By 32 weeks gestation, as recalculated by Windsor & Orleans (1986), 27% of the experimental group were ex-smokers, as verified by the measurement of thiocyanate in saliva.

It is well known that most smokers want to stop smoking but they usually decline clinical treatment (Windsor *et al.* 1985; Hughes *et al.* 1982; Windsor & Orleans 1986). To find methods accepted by most smokers, even if the success rates are low, might be of more value than finding more efficient but exclusive ones.

The aim of this trial was to study the effect of a method which required minimal involvement of personnel and was accepted by a large number of smokers.

Subjects and methods

Experimental design

Thirteen of the 14 public health maternity clinics in Gothenburg took part in the study. During one year (1 March, 1987 to 28 February, 1988) all pregnant women attending a maternity clinic for their first visit were asked about their smoking habits by a midwife, who also advised smokers to stop smoking.

Inclusion criteria for the study were pregnant women registered as daily smokers (at least one cigarette/day), with a gestational age of less than 12 weeks, and who spoke Swedish. Overall 745 women were eligible for inclusion in the study. At the next appointment, about 2 weeks later, they were asked again about their smoking consumption, this time by the obstetrician. At that point 22 women (3%) had stopped smoking, the remaining 723 women were randomized in the following way. Women born on days 1–10 of every month formed the control group ($n = 231$), and those born on days 11–31 formed the treatment group ($n = 492$). The uneven randomization was used because we expected a large number of refusals in the treatment group.

The women in the control group were given an information sheet by their doctor with basic facts about smoking and pregnancy and a recommendation to stop smoking. The same information was included as was given in the last pages of the self-help manual.

In the treatment group the women were offered a self-help manual on stopping smoking. The manual was written especially for pregnant women. The manual developed by Windsor *et al.* (1985) served as a model but was thoroughly revised and new parts included. The first version was tested in a pilot study and then revised slightly. The programme in the manual was divided in two phases, a preparatory and a cessation phase. The preparatory phase lasted for one week. The smoker was given new assignments every day to the quit day. The tasks were based on the principles of behaviour therapy. They consisted of, for example, nicotine fading, recognizing smoking situations, saving nasty smelling cigarette butts, learning how to relax, and preparing to meet the urge to smoke. The cessation period was followed for the first 5 days with new information daily. It included the most common abstinence problems and how to cope with them, concrete advice for specified situations, and relapse prevention counselling. The last pages contained basic facts about smoking and pregnancy

The manual was distributed by the obstetrician to the 417 women who agreed to participate; 75 (15%) refused to take part in the study.

Table 1. Characteristics of the subjects at randomization

Characteristic	Treatment group Total	 Participants	 Refusers	Control group
No of subjects	492	417	75	231
Mean age (years)	28·4	28·3	28·9	28.6
No of cigarettes/day				
Mean	16·8	16·8	16·1	16·4
95% CI	16·3–17·3	16·5–17·1	15·3–16·9	15·7–17·2

Measurements

Smoking consumption was recorded at the first visit, at 12–14 weeks, at 30–34 weeks, and about 8 weeks after delivery. The women were interviewed by a midwife except for the randomization visit at 12–14 weeks, when an obstetrician conducted the interview. The current number of cigarettes and the brand was noted. At their first visit, women were asked about their cigarette consumption before pregnancy and at their last follow-up they were asked if they had smoked during their 4–5 day stay in the maternity ward.

To verify that they were not smoking, blood thiocyanate was measured at 30–34 weeks and at the post partum visit, using the method described by Lundquist *et al.* (1979). The cut-off limit was 100 ng/ml (Windsor 1985).

Subjects

The quit rate in the control group was estimated at 4%, and about 12% in the treatment group. In order to detect a statistically significant difference at a 5% level with a power of 80%, the size of the groups should be at least 170 women.

The mean age of the 492 women in the treatment group was 28·4 years compared with 28·6 years in the 231 women in the control group. The 75 women in the treatment group who refused to participate did not differ in age (mean 28·9 years) from the participants. The initial cigarette consumption was about 16 cigarettes per day and did not differ between the groups (Table 1).

Attrition owing to miscarriage, later refusal to participate, and moving out of the district was 10% in the control and 11% in the treatment group. These women were excluded from the results. Data missing for other reasons were counted as failures At the three follow-up points the missing data figures were 8%, 9% and 16% in the treatment group compared with 5%, 11% and 19% in the control group.

Women who claimed not to be smokers were counted as smokers if their thiocyanate value was above the cut-off level. For the primary analysis the women remained in the group to which they were originally randomized.

Statistical tests

Comparisons between the groups were made with the *t*-test and by calculation of 95% confidence intervals and odds ratio. In multiple comparisons, analysis of variance with Duncan's test was used. The significance level was set at 5%.

Results

More women stopped smoking in the treatment group than in the control group (Table 2). At the

Table 2. Smoking cessation rates in the two groups

	Women who stopped smoking Treatment group ($n = 444$)	 Control group ($n = 209$)	Odds ratio (95% CI)
Continuously abstinent	46 (10·4)	11 (5·2)	0·5 (0·2–0·9)
Week 30–34	56 (12·6)	18 (8·6)	0·7 (0·4–1·1)
At hospital	134 (30·2)	51 (24·4)	0·8 (0·5–1·1)
8 weeks after delivery	70 (15·8)	19 (9·1)	0·5 (0·3–0·9)

Table 3. Cigarette consumption in the two groups

	No of cigarettes/day			
	Treatment group ($n = 444$)		Control group ($n = 209$)	
	Mean	(95% CI)	Mean	(95% CI)
Before pregnancy	16·7	(16·2–17·2)	16·3	(15·9–16·7)
At first visit	10·8	(10·3–11·3)	10·8	(10·4–11·2)
Week 12–14	10·3	(9·8–10·8)	10·2	(9·8–10·6)
Week 30–34	9·3	(8·6–9·8)	9·6	(9·2–10·0)
(ex-smokers excluded)	10·7	(10·1–11·3)	10·6	(10·3–11·0)
8 weeks after delivery	9·1	(8·5–9·7)	10·0	(9·6–10·4)
(ex-smokers excluded)	11·2	(10·6–11·8)	11·3	(11·0–11·6)

post partum examination the number of ex-smokers was statistically significantly greater in the treatment group.

Smokers relapsed and stopped smoking again during the assessment period. Those who were ex-smokers at all three follow-up points were reported as continuously abstinent. This criterion was met in 10% of the treatment group compared with 5% of the control group. The difference was statistically significant.

Cigarette consumption did not differ significantly between the control and the treatment groups during the assessment period (Table 3). Those who were offered the manual but refused to participate had the same cigarette consumption (95% CI 14·5–17·7 cig/day) before pregnancy as those who agreed to participate. However, at the first visit to the maternity clinic (95% CI 8·4–10·6 cig/day) and at the time of randomization (95% CI 7·3–9·5 cig/day), the refusers had reduced consumption, and smoked statistically significantly fewer cigarettes per day than those who accepted treatment and those in the control group (Duncan's multiple comparison test).

Women decreased their smoking consumption by about 40% between the pre-pregnancy period and the first trimester; *t*-test values after paired observations between cigarette consumption before pregnancy and at 12–14 weeks were 15·6 in the control group, and 21·4 in the treatment group respectively. The reductions were all significant at 5% level.

If the women who stopped smoking are excluded from the numbers in Table 3, the mean number of cigarettes per day for those who continued to smoke slowly increased from 10·7 at 30–34 weeks to 11·2 after delivery in the treatment group and from 10·6 to 11·3 in the control group, the difference between the two groups was not statistically significant.

The mean birthweight in the treatment group (3430 g, 95% CI 3378–3483 g) was higher than in the control group (mean 3359 g, 95% CI 3286–3433 g). The proportion of women delivered before 36 weeks gestation was lower in the treatment than in the control group and the proportion of low birthweight babies (<2500 g) was also lower in the treatment group. However, none of the differences was statistically significant (Table 4).

Discussion

More than 10% of the women in the treatment group stopped smoking during pregnancy and were still not smoking 8 weeks after delivery. There were twice as many women in this group who abstained from cigarettes as in the control group. The results might be compared with those of Windsor *et al.* (1985) With a method similar to ours, they reported that 14% stopped

Table 4. Gestational age and birth weight in the two groups

Variable	Treatment group *n*	(%)	Control group *n*	(%)	Odds ratio (95% CI)
Delivery <36 weeks	13/421	(3·1)	8/197	(4·1)	0·8 (0·3–1·8)
Birthweight <2500 g	14/422	(3·3)	11/198	(5·6)	0·6 (0·3–1·3)

smoking. However, our follow-up period was 2 months longer, which makes a comparison between the studies difficult.

Both Ershoff *et al.* (1983) and Sexton & Hebel (1984) had higher success rates with their methods than we found in our study. However, their methods were more time and personnel-consuming.

Most women reduce their cigarette consumption when they are pregnant. The reduction was greatest during the first months. In our study, consumption remained fairly stable after 12 weeks. Eight weeks after delivery cigarette consumption was still reduced. According to Windsor & Orleans (1986) most women who stop smoking or reduce their consumption go back to their usual habits late in pregnancy or after delivery. This was not found in our study. A reduction in the number of cigarettes smoked remained, even if there was a slight increase in cigarette consumption among those who did not stop smoking.

It is noticeable that 25–30% of the women refrained from smoking during their hospital stay. This was the highest figure for the whole period of assessment. Obviously the time after delivery is a period when many women try to stop smoking. This should be recognized so that appropriate support can be given at this time.

The total number of quitters depends not only on the efficacy of a method but also on its acceptance rate. Most studies lack information about this point. Windsor *et al.* (1985) reported an acceptance rate of 80%. In our study 85% were willing to use the self-help manual and this is a high rate.

Only a minority of smokers are prepared to attend clinics for help with stopping smoking. Even if the success rates are high the actual influence on a specific population is low. On the other hand, a handbook, such as ours, that is accepted by a majority (85%) means that even with a lower success rate the number of smokers that quit smoking will be higher. A further advantage of the self-help manual is a lower costing as administration requires less involvement of personnel.

Stopping smoking during pregnancy and postpartum has considerable potential for improving obstetric results and general health. All progress in this area must be considered valuable.

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Scar rupture in labour after previous lower uterine segment caesarean section: the role of uterine activity measurement

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Summary. A series of 12 trials of scar associated with scar rupture is reviewed. Uterine activity patterns were assessable in 10 of them. Clinical features and characteristics of the intrauterine pressure waveform and uterine activity are discussed in relation to the integrity of the scar.

Trial of scar, after previous lower uterine segment incisions for caesarean section, can be managed successfully providing care is taken in the selection of such pregnancies. Vaginal delivery has been achieved 60–70% (Gibbs 1980; Eglinton *et al.* 1984) and some workers would maintain that oxytocin can be safely administered, providing uterine activity is carefully monitored and controlled (Phelan *et al.* 1987, Arulkumaran *et al.* 1989b). However, the scar is a potential site of weakness and scar rupture during trial of scar has been reported in 0·3–0·7% (Lavin *et al.* 1982; Phelan *et al.* 1987).

Though the normal limits for uterine activity during trials of scar associated with successful outcomes have been reported (Arulkumaran *et al.* 1989a; Arulkumaran *et al.* 1989b), these data reflect, by definition, the behaviour of a scarred but intact uterus. Uterine activity, however calculated, is derived from intrauterine pressure measurements and this is determined by uterine wall tension. Since the scar is part of the uterine wall, it acts as a potentially compliant element in series with the cervix. Therefore, weakness or compliance in the scar should modulate wall tension reducing intrauterine pressure and uterine activity (Gee *et al.* 1988). Thus theoretically, the behaviour of the scar introduces an unpredictable variable which casts doubt upon the veracity of transferring uterine activity data collected from labours in which the scar is intact to those in which its behaviour is pathological and unpredictable.

Before one can rely on intrauterine pressure monitoring for the safe conduct of trial of scar it is first essential to know whether scar rupture can occur even if uterine activity is maintained within normal limits. First, if it can, UA monitoring, by itself, does not offer a safeguard and, second are there any features of the intrauterine pressure recording which could preempt the rupture? In an attempt to answer these questions we conducted a retrospective analysis of uterine activity in trials of scar associated with scar rupture.

Subjects and methods

The case codings of deliveries at the Birmingham Maternity Hospital for years 1982–1988 were reviewed Case notes coded for trial of scar were retrieved. Where scar rupture was confirmed at operation, the case notes were scrutinized for clinical details, intrauterine pressure measurements and uterine activity.

Intrauterine pressure was recorded using

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Sonicaid FM3R monitors, external transducers (Medex) and fluid filled catheters (Portex). The use of this equipment was in accord with manufacturers' instructions and current clinical guidelines for the siting of catheters and transducers and the regular flushing of catheters were observed (Odendall *et al.* 1976).

Uterine activity integral (UAI) (Steer 1977) was used for the assessment of uterine activity and the value UAI (max) used for the interpretation of data was the highest uterine activity recorded over at least two consecutive 15 min epochs before scar rupture.

Oxytocin, when used, was titrated against uterine activity using an arithmetic regimen starting at 2 mU/min and increasing by 2 mU every 15 min to a maximum of 32 mU/min.

Results

Trial of scar was successful, resulting in a vaginal delivery, in 65%. There were no maternal or perinatal deaths.

Twelve lower uterine segment scar ruptures were confirmed by operative exploration. This represents a scar rupture rate of 1 in 145 (0·7%) trials. One of these trials was not monitored by intrauterine pressure catheter and therefore was unsuitable for full assessment and another scar rupture was diagnosed after a rotational forceps delivery. Since operative trauma could not be discounted in this patient she was also excluded from the analysis. We therefore have full data for 10 scar ruptures associated with trial of scar (Table 1).

Four scar ruptures were considered to have taken place spontaneously at full dilatation or in the second stage. The other six occurred in the first stage. All the women had had only one previous section and only one of the ten sections had been elective, most were performed for fetal distress ($n = 6$). For nine of the ten sections the indications for section had been clearly unrepeatable and no factors indicated an increased risk of scar rupture. In one woman (no. 2) where the indication for previous caesarean section had been 'failure to progress', X-ray pelvimetry had excluded a contracted pelvis.

In four women labour had been induced by prostaglandins (one orally and three vaginally). It may be postulated, on theoretical grounds, that prostaglandins could have two adverse effects: they potentiate oxytocin and they may weaken the connective tissue of the scar. Only in one (no. 8) of the three women induced with vaginal prostaglandin was scar rupture associated with uterine activity levels above those normally recorded in trials with successful outcomes. If the scar were to be weakend by prostaglandins, rupture may be expected early, as soon as contractions were applied. However, two out of these three ruptures occurred in the second stage and only one in the first stage.

Six labours were augmented with oxytocin.

Table 1. Clinical characteristics of 10 women with scar rupture in labour in their second pregnancy after previous lower segment caesarean section (LSCS)

							Outcome	
Subject no.	Indication for LSCS	Labour induction	Oxytocin	UAI_{MAX} (kPas/15m)	Symptoms/ signs	Timing of rupture	5-min Apgar score	Birthweight (kg)
1‡	Cord prolapse	No	Yes	1500	FD/FTP	3 cm	10	3·62
2‡	FTP	No	No	1500	Uterus odd shape	6 cm	9	3·58
3‡	FD	No	No	2100*†	Fetal tachycardia	6 cm	9	2·84
4‡	FD PE	Vag PG	Yes	1750*	Pain	6 cm	9	3·56
5	FD	Oral PG	Yes	1250	Vaginal bleeding	5 cm	9	3·70
6	FD	SROM	Yes	1800*†	FTP	3 cm	9	3·75
7	FD	No	Yes	2400*†	FD/haematuria	Stage 2	5	2·60
8	FD	Vag PG	Yes	2500*†	FD	Stage 2	9	3·62
9	FD	No	No	1700*	Pain	Stage 2	9	3·37
10	Elect Breech	Vag PG	No	1200	FD	Stage 2	5	2·34

* Above limits of uterine activity advised by Steer (1977).

† Above limits of uterine activity described by Arulkumaran *et al* (1989a)

‡ CTG illustrated in Fig 1

Abbreviations. FD, fetal distress, FTP, failure to progress; PG, prostaglandin, UAI_{MAX}, highest uterine activity integral, SROM, rupture of membranes; PE, pre-eclampsia

Precise ranges for uterine activity in these circumstances is difficult to interpret. Four of the six augmented labours had uterine activity levels above those advised by Steer (1977) but only three were above the levels recorded by Arulkumaran *et al.* (1989a & b) in successful trials. Furthermore, by the same criteria abnormally high uterine activity levels were recorded in one woman (no. 3) who had a spontaneous unaugmented labour. These interpretations of uterine activity levels have been made after due consideration of the patient's obstetric history (Arulkumaran *et al.* 1989a), the stage of labour at which the rupture occurred and the use of oxytocin (Arulkumaran *et al.* 1989b) since all of these factors affect the range of uterine activity.

In four trials scar rupture occurred during the first stage and no manipulation of uterine activity had been undertaken. The recordings from these four labours are shown in Fig. 1. Theoretically, loss of wall tension due to scar rupture should produce a reduction of contraction amplitude while duration and repetition frequency remain constant (Gee *et al.* 1988). These effects are seen in practice as a 'clipping off' of the contraction peaks. The fall in UAI (recorded as 'bars' on the tocograph) results from this fall in amplitude, not from changes in duration and repetition frequency which remain the same.

Discussion

The first question posed in the introduction is easily answered. Six of these scar ruptures occurred even when the uterine activity was within the normal limits described by Alkumaran *et al.* (1989a & b) for trial of scar and by Gibb *et al.* (1984) for spontaneous normal labour, and four were within the limits advised by Steer (1977). Indeed, rupture may occur with relatively low levels of activity (nos. 5 and 10). This paradox can be explained in terms of the

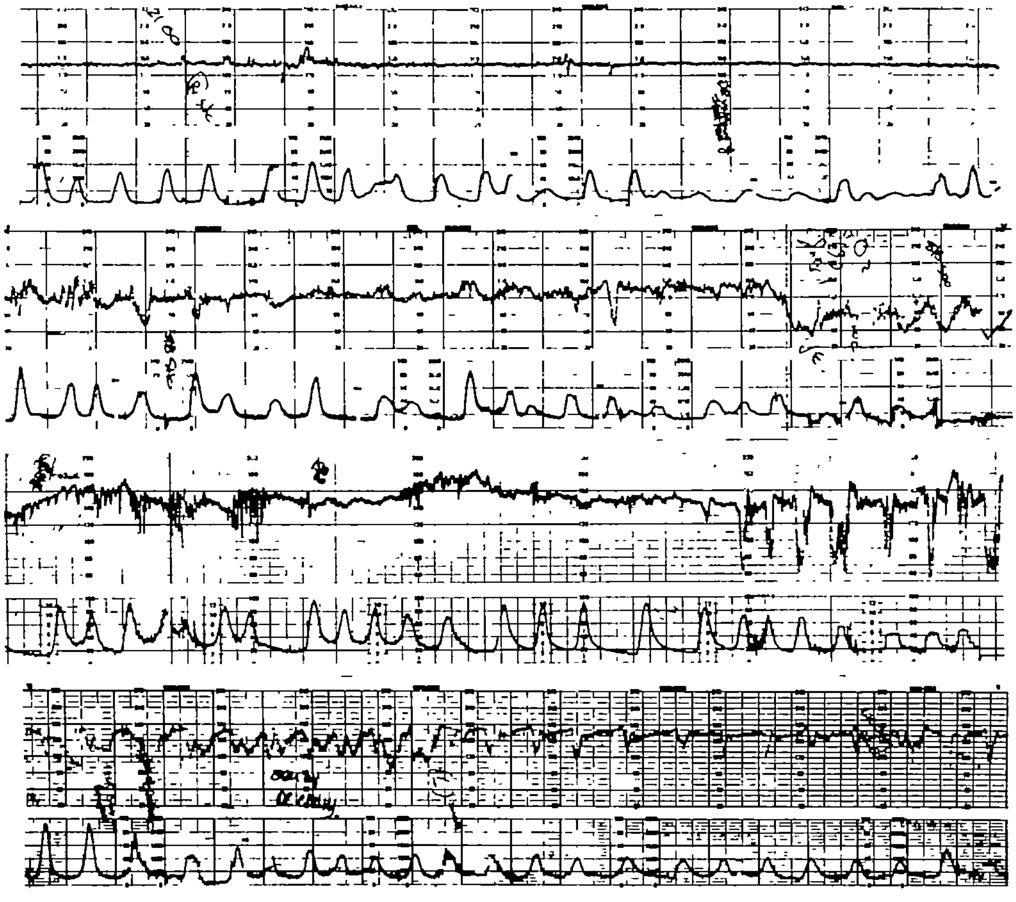

Fig. 1. Cardiotocographic recordings in four women (nos 1–4 in Table 1) with scar rupture in the first stage of labour after previous lower segment caesarean section.

weakening scar decreasing wall tension resulting in low levels of recorded intrauterine pressure. Thus, reliance on pressure monitoring could give the wrong impression unless there is a clear physiological understanding of the system being monitored. Since scar rupture occurs infrequently, it is misleading to imply that the association between 'normal' levels of uterine activity and 'safe' outcome is causally related. The association may only be fortuitous, requiring a much larger series than reported to detect those where the outcome is not so straightforward.

The reduction in wall tension produced by the yielding scar may also result in reduced transmission of tension to the cervix resulting in suboptimal cervical dilatation. Downward modulation of wall tension from a weak scar producing low intrauterine pressure and poor cervical dilatation could result in the clinician wrongly ascribing poor progress to ineffective uterine activity. As a result oxytocin may be administered in an attempt to restore uterine activity and progress to normal. In so doing more stress would be applied to the scar, hastening its rupture.

Three of the six trials stimulated with oxytocin had high uterine activity compared with only one of the four that were not augmented. This would suggest that care must be taken when oxytocin is used and it may be prudent to use the lower limits of uterine activity advised by Steer (1977). However, the third highest activity level occurred in a spontaneous, unstimulated labour. It is difficult to see how this pattern of activity could have been manipulated to conform to preset limits. Two of the highest activities (also associated with oxytocin stimulation) were recorded at the end of the first stage before scar rupture occurred in the second stage. Arulkumaran *et al.* (1989a) reported that uterine activity normally rises towards the end of the first stage and this natural effect, rather than the oxytocin stimulation *per se,* may account for these high recordings. Nevertheless, careful attention to uterine activity as labour progresses is advised, enabling significant reductions in oxytocin dosage and avoiding overstimulation.

The second question, namely the occurrence of any feature on pressure monitoring which could help to pre-empt scar rupture, is more difficult to answer. The accepted symptoms and signs of scar rupture, that is to say, FHR abnormalities, vaginal bleeding, failure of the cervix to dilate, irregularity of the uterus and pain over the scar were evident in various combinations, the most common single feature being FHR abnormality. The problem with these features is that they are all seen *after* the event rather than before. Cessation of contractions has also been reported but has been refuted by pressure monitoring data (Rodriguez *et al.* 1989). In the four recordings shown in Fig. 1, a marked fall in uterine activity is seen, characteristically with a 'clipping' off of the pressure peaks, as predicted by the theoretical analysis of intrauterine pressure generation (Gee *et al.* 1988). This feature may start before FHR abnormalities can be identified.

We conclude that intrauterine pressure monitoring is not, of itself, a safeguard against scar rupture. However, it is prudent to guard against overstimulation when oxytocin is being used In these circumstances pressure monitoring may be of value, particularly towards the end of the first stage when there is a natural tendency for the intrauterine pressure to rise. Reduction in oxytocin dosage at this time may avoid undue stress on the scar. The way the scar modulates wall tension under pathological circumstances is of crucial importance. The waveform characteristics demonstrated in associated with scar rupture due to the scar's modulation of wall tension should be noted also, but these features may still not give much of a 'lead time' in diagnosis. Intrauterine pressure monitoring should not be a substitute for, nor be an over-riding factor in, the overall clinical appraisal of the trial of scar.

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Lactation inhibition by the dopamine agonist CV 205–502

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Summary. In an open pilot study with a parallel group design 30 bottle feeding women were randomly assigned in a two to one ratio to receive either the new dopamine agonist CV 205–502 or bromocriptine for lactation inhibition. Ten women who intended to breast feed served as normal controls. All treated women reached prepregnant prolactin levels within 72 h with once-daily 0·075 mg of CV 205–502 or twice-daily 2·5 mg of bromocriptine, at starting doses of 0·05 mg and 2·5 mg respectively. Fifteen of the 20 women treated with CV 205–502 reported breast symptoms, 50% occurring on days 3 and 4 of treatment. Three of the 10 women treated with bromocriptine had breast symptoms between days 2 and 28. Overall efficacy and tolerance in the two groups was very good. Side effects did not differ between the groups, with the exception of pulse rate in the standing position, which was significantly higher in the bromocriptine treated group than in either the CV 205–502 group ($P = 0{\cdot}02$) or the breast feeding group ($P<0{\cdot}01$). The coagulation tests (fibrinogen, AT III, PTT and APTT) showed no significant differences between the three groups.

There are many reasons why puerperal lactation may need to be inhibited, social reasons being the most common (Eastham *et al.* 1976; Bacon & Wylie 1976). Effective suppression of puerperal lactation had long been a problem until the introduction of the dopamine agonist bromocriptine in the 1970s (Varga *et al.* 1972; Rolland 1979; Duchesne & Leke 1981; Rolland & Schellekens 1973), but several recent reports have implicated bromocriptine in various side effects in the puerperium (Iffy *et al.* 1986; Katz *et al.* 1985; FDA Drug Bulletin 1984; Watson *et al.* 1989).

The non-ergot dopamine agonist CV 205–502 is an octahydrobenzo[g]quinoline (Nordman & Petcher 1985) which has demonstrated strong prolactin lowering effects in various animals, in healthy volunteers and in hyperprolactinaemic patients (Gaillard *et al.* 1986; Rasmussen *et al.* 1987; Heijden *et al.* 1988; Rasmussen *et al.* 1988). Approximately 80% of the hyperprolactinaemic patients treated during a dose-titration study achieved normal prolactin levels with once daily doses of CV 205–502 between 0·05 and 0·10 mg (Heijden *et al.* 1989). The drug has been generally well tolerated, and reported adverse effects have been transient nausea, sleepiness and headache during the initiation of therapy

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(Heijden *et al.* 1988). Since studies so far indicate that the drug is safe (ECG recordings, physical and laboratory blood and urine tests) it was expected that the strong 24 h prolactin suppressant properties of CV 205–502 should offer an effective and well accepted alternative for use in inhibition of puerperal lactation.

Therefore it was decided to study prospectively the clinical and prolactin suppressant effects of a once-daily dose of CV 205–502 in the prevention of postpartum lactation. A parallel group received a twice-daily dose of bromocriptine (Parlodel®, Sandoz Ltd, Basle). The safety of CV 205–502 was assessed by way of standard laboratory blood tests, selected measures of coagulation and fibrinolysis and physical and ECG examinations. The assessment of vital signs, coagulation and fibrinolysis was also performed in the bromocriptine treated patients and in a control group of 10 normal women who intended to breast feed.

Subjects and methods

Study design

In this first study to test CV 205–502 in the suppression of postpartum lacation, an open model was chosen to examine two aspects of the suppression of postpartum lactation: (i) to find the optimal dose of CV 205–502 and to compare its effect with that of bromocriptine both clinically and on plasma prolactin levels; (ii) to assess the safety of CV 205–502 by means of ECG and laboratory urine and blood tests, including tests of coagulation and fibrinolysis.

A two to one ratio was chosen to receive either CV 205–502 (20 women) or bromocriptine (10 women). The patients and investigative staff were aware of the treatment of each patient. Ten women who intended to breast feed were selected to serve as normal controls for vital signs and tests of coagulation and fibrinolysis. The study had been approved by the ethics committee of the hospital and all women gave their written informed consent to participate.

All women had regular menstrual cycles previous to their pregnancies and had conceived spontaneously. They had no problems during the pregnancy and were delivered between 37 and 43 weeks gestation. None of the women used medication which could interfere with the administered dopamine agonists, and intake of oral contraceptives was to be delayed until day 42 postpartum.

The treatment was started within 24 h after delivery. In the CV-group, CV 205–502 was given as a daily oral dose at bedtime of 0·05 mg (day 1), 0·075 mg (days 2–14) and 0·05 mg (days 15–21). In the bromocriptive-group, bromocriptine was given twice daily 2·5 mg (days 1–14), followed by once daily 2·5 mg (days 15–21) to prevent rebound lactation (Rolland & Schellekens 1973). If breast tenderness or milk production was recorded at any time after day 4, the bedtime dose of CV 205–502 could be increased to 0·125 mg up to day 14 and a further dose increase of 0·05 mg daily could be given if necessary.

Assessment

The patients were visited for assessment on days 0 (day of delivery), 1, 2, 3, 4, 6, 9, 12, 15, 18, 22, 24, 28, 35 and 42. On these days blood samples were obtained to estimate prolactin (PRL) levels. The women were questioned about breast symptoms (milk production, congestion and pain) and side effects. The following rating scale was used: none, mild, moderate (no treatment required) and severe (treatment required). The amount of milk secretion was classified as follows: none, mild (few drops), moderate (spontaneous secretion) and severe (stream of milk). These daily observations were graded according to the severity and duration of the symptoms as follows: very good, no symptoms or mild short-lasting symptoms (<24 h); good, mild long-lasting symptoms (>24 h) and/or moderate short-lasting symptoms (<24 h); moderate, moderate long-lasting symptoms (>24 h) and /or severe short lasting symptoms (<24 h), poor, severe long-lasting symptoms (>24 h). The safety of CV 205–502 was tested by routine physical examination, ECG and laboratory tests (haemoglobin, platelets, leucocytes and differential count, urea, creatinine and liver enzymes) on days 0 and 42. Coagulation tests, fibrinogen, activated partial thromboplastin time (APTT), prothrombin time (PTT) and antithrombin III were performed on days 0, 1, 12 and 42. Pulse rate and blood pressure were recorded at each visit in the supine position and after 3 min standing to examine the possible presence of orthostatic hypotension. The Spectria competitive solid-phase RIA from Farmos Diagnostica (Turku, Finland) was used for measuring PRL (sensitivity: 30 mIU/l and inter-assay variation: 9%).

Statistics

The Wilcoxon rank sum test was used to analyse the PRL results and other laboratory findings. Fisher's exact test was used to compare the clinical results. Differences with $P<0{\cdot}05$ were considered significant.

Results

Four women started to take oral contraceptives before day 42 post partum, two in the CV-group (days 15 and 26) and two in the bromocriptine-group (days 22 and 30). When all data were examined including or excluding the findings or measurements in these four women, the results remained the same, so data from these women are included.

The characteristics of the women in the three study groups are given in Table 1, there were no significant differences between the groups.

Prolactin

Fig. 1 summarizes mean prolactin concentrations in the three groups: both CV 205–502 and bromocriptine suppressed prolactin to the normal prepregnant range (<750 mU/l) within 72 h. Bromocriptine-treated women tended to normalize more rapidly. The calculated mean half life for prolactin suppression in the bromocriptine-group was 0·59 h (SD 0·43) and 0·87 h (SD 0·33) in the CV-group ($P = 0{\cdot}09$). In both groups a rebound phenomenon occurred after withdrawal of the drugs on day 21. In the bromocriptine-group also an increase of prolactin from day 14 onwards was obvious after dose reduction. From day 35, all prolactin measurements were within the normal range. The prolactin profile in breast feeding women was quite different with a gradual decline until day 28, with clearly elevated levels thereafter. The initial period was characterized by fluctuating levels in each woman. Blood sampling for prolactin measurement was not related to time of breast feeding.

Efficacy

Three of the 10 women in the bromocriptine-group and 15 of the 20 women in the CV-group reported breast symptoms. In the bromocriptine-group symptoms were recorded for 1 to 3 days. In the CV-group, six women had symptoms for 1 day, six had symptoms for 2 days, two had symptoms for 3 days and one had symptoms for 4 days. Although the woman had moderate symptoms the dose was increased and the complaints disappeared. In one other woman the dose was increased after 3 days of increasing complaints. In the CV-group more than 50% of the complaints occurred during days 3 and 4 whereas in the bromocriptine group the complaints were much more spread out between days 2 and 28. No rebound lactation took place after cessation of medication. The final assessment of overall efficacy for the 20 women in the CV-group was very good in 12, good in six women, moderate in one, and poor in one (Fig. 2). In the bromocriptine group eight women graded their symptoms as very good and the other two as moderate. The difference between the groups was not significant ($P = 0{\cdot}54$).

Table 1. Characteristics of the women in the three study groups

Variable	CV 205–502 ($n = 20$)	Bromocriptine ($n = 10$)	Breast-feeding ($n = 10$)
Age (years) mean (SE)	28·3 (0·8)	27·3 (0·9)	30·4 (1·1)
Parity			
Primiparae	8	5	8
Multiparae	12	5	2
Mode of delivery			
Vaginal	18	8	8
Abdominal	2	2	2
Gestational age at delivery (weeks)			
37	2	1	1
38	3	1	–
39	2	–	3
40	6	5	5
41	6	3	–
42	1	–	–
43	–	–	1

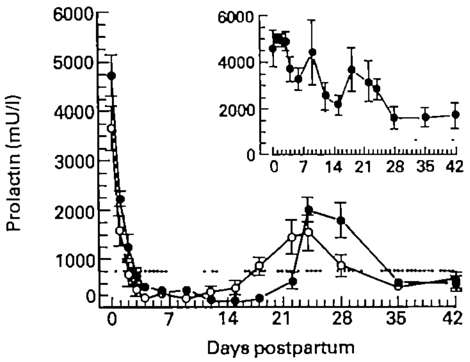

Fig. 1. Mean serum prolactin (mIU/l ± SEM) values during CV 205–502 (—○—) and bromocriptine (—○—) treatment. Inset: mean serum prolactin (mIU/l ± SEM) values in the breast feeding group.

Side-effects

In both groups side effects were reported, mostly of mild intensity and none of the participants withdrew from the study because of side effects. Figure 2 summarizes the overall tolerance and there was no significant difference between the two groups ($P = 0{\cdot}54$). In the CV-group 10 of 20 women reported side effects; headache (4), dizziness (3), nausea (4), vomiting (1) and insomnia (1). One of these 10 women complained of nausea and vomiting on days 3 and 4, which resulted in interruption of treatment for 1 day (day 4). She was delivered by caesarean section and the complaints were attributed to the presence of bowel distension. Dizziness and nausea were reported at initiation of therapy whereas headache was reported even after cessation of medication by two women. Three of 10 women in the bromocriptine-group reported side effects: headache (2), dizziness (2) and nausea (1). In this group also dizziness and nausea occurred at initiation of therapy.

Safety

In the supine position blood pressure (systolic and diastolic) and pulse rate did not show significant differences between the three groups. After 3 min of standing blood pressure remained unchanged in all groups whereas pulse rate increased. There was no significant difference in the pulse rate on standing between the breast feeding control group and the CV-group ($P = 0{\cdot}24$), but the women in the bromocriptine-group had a significantly higher pulse rate on standing than the control group ($P<0{\cdot}01$) or the CV-group ($P = 0{\cdot}02$).

Table 2 summarizes the changes in coagulation and fibrinolysis variables. The values obtained on days 0 (before drug intake) and 42 are compared; the values on days 1 and 12 did not differ significantly from those on day 0 (all P-values $>0{\cdot}02$) and they are not shown. There was no significant difference between the three groups on day 0 and day 42. The postpartum period was characterized in all women by a decrease in fibrinogen ($P<0{\cdot}02$) and an increase in antithrombin III ($P<0{\cdot}04$); APTT tended to increase but this change was signficant only in breast feeding women ($P = 0{\cdot}03$). PTT remained constant.

The results obtained from routine haematology and blood chemistry in the CV-group did not show significant differences between days 0 and 42. The most persistent finding was a highly significant decrease of creatinine phosphokinase (CPK) in all women (day 0: mean 210, SD 130 units, day 42: mean 70, SD 80; $P<0{\cdot}01$).

In the CV-group, ECG recordings on day 0 were normal in 18 women and one woman had slight tachycardia with flattened T waves, on day 42 all women had normal ECG recordings. A full general examination on days 0 and 42 did not show any changes which could be attributed to the use of CV 205–502.

Discussion

Previous studies have shown dopamine agonists like bromocriptine to be effective in the inhibition or suppression of lactation (Rolland 1986). In the present study bromocriptine showed the well known profile of rapid suppression of prolactin concomitant with nearly complete inhibition of mammary activity.

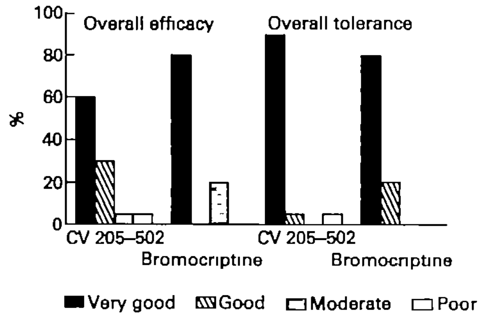

Fig. 2. Overall efficacy and overall tolerance as judged by the investigator in the CV 205–502 and bromocriptine treated groups.

Table 2. Comparison of coagulation and fibrinolysis tests on day 42 versus day 0

	CV 205–502			Bromocriptine			Breast feeding		
	n	Mean*	(SEM)	*n*	Mean*	(SEM)	*n*	Mean*	(SEM)
Fibrinogen (g/l)	18	−1·06	0·16	7	−1·37	(0·2)	10	−1·28	(0·33)
AT III (%)	18	8·7	1·9	8	5·0	(1·5)	10	10·5	(3·3)
PPT (s)	18	0·2	0·4	8	−0·4	(0·4)	10	0·0	(0·4)
APTT (s)	18	4·8	1·4	8	2·3	(1·8)	9	3·9	(1·7)

*Mean difference.

n, number of measurements, AT III, antithrombin III, PPT, prothrombin time, APTT, activated partial thromboplastin time.

The new dopamine agonist CV 205–502 was very similar in its profile: rapid prolactin suppression and inhibition of mammary activity. The difference between these two drugs, which was not statistically significant, was the more rapid normalization of prolactin levels in the bromocriptine treated women. This may explain why the women in the CV-group who reported signs of mammary activity tended to do so on days 3 and 4. This suggests that the initial dose of 0·05 mg of CV 205–502 was slightly too low and should be increased to 0·075 mg. Indeed 0·075 mg has been recommended as a starting dose in gynaecological patients suffering from symtomatic hyperprolactinaemia (Heijden *et al.* 1989).

After withdrawal of the drugs on day 21 a significant prolactin rebound release was obvious in both groups. In the bromocriptine-group this rebound release already began on day 14 when the drug dosage was decreased. The difference in the patterns of the two curves, a sharper rise in the CV-group and a more flattened curve in the bromocriptive-group, indicates that after acute inhibition of pituitary prolactin release, an easily releasable prolactin pool remains in the lactotrophes for at least 3 weeks (Vemer & Rolland 1981; Pasteels *et al.* 1971). Despite this rebound release, however, no signs of rebound mammary activity were seen. Shorter suppression of prolactin has been reported to result in rebound lactation in a substantial percentage of women (Rolland & Schellekens 1973). The mammary gland after 3 weeks of prolactin suppression is less responsive to prolactin. An explanation for this may be the fact that around day 21 in dopamine agonist treated women, ovarian activity is restored, with many women actually experiencing their first ovulations during this period (Kremer *et al.* 1989). High levels of circulating 17β-oestradiol, possibly in combination with progesterone, protects the mammary epithelium from the stimulating effect of prolactin (Thomson *et al.* 1975).

In this study only mild side effects of headache, nausea, dizziness and insomnia were reported in some women in both groups except for one woman with bowel distension on days 3 and 4 after an abdominal delivery. These findings are in agreement with previous reports that postpartum women tolerate dopamine agonists very well (Rolland & Schellekens 1978).

Of great interest is the statistically significant increase in pulse rate seen in the bromocriptine treated women compared with the CV-group and breast feeding women although there was no significant change in blood pressure. This may indicate that bromocriptine exerts a haemodynamic effect, which was absent following CV 205–502 treatment and in the breast feeding women. This finding may be seen as a tendency to orthostatic hypotension in bromocriptine-treated women which was counteracted by the increase in pulse rate. CV 205–502 treated women behave in this respect like breast feeding women indicating that this drug has little or no influence on the cardiovascular system. This is in agreement with findings in volunteers and in hyperprolactinaemic patients in whom no influence on blood pressure and pulse rate was found (Gaillard *et al.* 1986; Rasmussen *et al.* 1987; Heijden *et al.* 1988; Rasmussen *et al.* 1988; Heijden *et al.* 1989).

There were no significant differences in changes in the clotting factors between the treated and control groups. Few data have been published on changes in the coagulation and fibrinolysis systems post partum. The observed changes, similar in all three groups, with a decrease in fibrinogen and an increase in antithrombin III indicates that the hypercoagulability present during pregnancy (Bonnar 1979) gradually disappears. Although it has been suggested that dopamine agonists could influence these indices unfavourably, this study clearly demonstrates that neither CV 205–502 nor bromocriptine influence coagulation and fibrinolysis.

Also in the CV 205–502 treated women no significant changes were observed in routine haematology and blood chemistry aside from the highly significant decrease of CPK from day 0 to day 42. This is explained by the uterine muscle strain during delivery and by the involution of the uterus thereafter. General physical examinations and ECG recordings in CV 205–502 treated women measured previous to and after treatment did not reveal any changes, also indicating the safety of CV 205–502 in postpartum patients.

It can be concluded that CV 205–502 is as effective as bromocriptine in the prevention of puerperal lactation. The drug has the advantage over bromocriptine that once daily administration is sufficient to produce normoprolactinaemia. Although the number of patients in our study is small, the findings are in agreement with other reports suggesting that CV 205–502 is a safe drug. The reported side effects were little different, but in our opinion the observed difference in haemodynamic changes between bromocritpine and CV 205–502 treated women and lactating women, would favour the use of CV 205–502. Our data indicate that further studies are necessary to identify the optimal starting dose, 0·05 mg seems to be too low. Therefore no definite conclusions on starting dose and safety of CV 205–502 in the indication of inhibition of lactation can be drawn with certainty from this study. Further prospective trials are needed to answer these questions.

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Continuation of normal neurobehavioural development in fetuses with absent umbilical arterial end diastolic velocities

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Summary. Detailed serial observations of behaviour were made in four singleton fetuses who were very small for dates and who had persistently absent umbilical artery end diastolic velocities for 2 to 9 weeks duration. All were born preterm for deteriorating maternal disease, and in two there were additional fetal indications for delivery. Behavioural comparison with 45 low risk singleton fetuses, at comparable gestations, revealed no significant differences in the development of behavioural cycles, the proportion of time spent in quiet cycles, or the amount of fetal breathing. None of the fetuses developed an abnormal heart rate pattern. We conclude that prenatal neurobehavioural development may continue apparently unimpaired in the presence of absent umbilical artery end-diastolic velocity of several weeks duration. Long term data of infant outcome are necessary before the clinical significance of this can be assessed.

Absence of end-diastolic velocities in the umbilical arteries and fetal aorta in the second half of pregnancy has been associated with increased perinatal morbidity and mortality (Rochelson *et al.* 1987; Hackett *et al.* 1987), and has been shown to precede the development of abnormal fetal heart rate patterns by several weeks in some cases (Rochelson *et al.* 1987). As yet there are no published data regarding the influence of abnormal flow patterns on neurobehavioural development, either in the short or long term.

We report here the findings of serial detailed behavioural observations on four fetuses with persistently absent umbilical artery end-diastolic velocities. We have compared the records with serial observations made at comparable gestational ages on 45 low risk singleton fetuses.

Subjects and methods

Two primigravid women whose fetuses were identified at 27 and 29 weeks respectively, as being clinically small for gestational age and with umbilical artery flow velocity waveforms (FVWs) showing absence of end-diastolic velocities (abnormal FVW), consented to participate in a longitudinal study of fetal behavioural development. Two multigravidas, with a past history of perinatal death associated with hypertension, who were already participating in a longitudinal study of behavioural development of high risk fetuses, were also found to have abnormal FVWs, namely very reduced umbilical artery end-diastolic velocities at 24 weeks and absent diastolic velocities from 27 weeks gestation

From the time of diagnosis of abnormal FVWs

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these four women underwent recording of fetal behaviour lasting 70 to 100 min every 5 to 7 days. Recordings were performed in a quiet room with the women seated in a comfortable semirecumbent position in a Parker Knoll chair. Initial measurements of fetal head circumference, abdominal circumference and largest pool of amniotic fluid in two perpendicular planes were made. Fetal eye movements, somatic movements, mouthing movements, diaphragmatic movements and heart rate pattern were recorded simultaneously using a standard fetal heart rate monitor (Hewlett Packard 8040A), and two realtime ultrasound transducers, one positioned to give a parasagital view of the fetal face (Siemens Sonoline SL1 with a 3.5 MHz transducer) and the other a transverse view of the fetal abdomen (Toshiba SAL 20A with a 2.4 MHz transducer). All observed movements were recorded on a polygraph (Hewlett Packard 7754A) using multiple hand held push buttons, together with a signal from the heart rate monitor to allow synchronizing of all variables. At the end of each study umbilical artery FVWs were recorded using a 4·0 MHz continuous wave transducer and a spectrum analyzer with a 100 Hz high pass filter.

The fetal behavioural findings were compared with those in 45 low risk singleton fetuses at comparable gestations, in whom the same behavioural variables were recorded at 4-week intervals throughout the second and third trimesters and who have been reported elsewhere (Pillai & James 1990a,b). In late pregnancy the fetus exhibits behavioural states which appear similar to some of the states described in newborn infants (Nijhuis *et al.* 1982). In the 45 healthy fetuses studied, the behavioural state criteria were fulfilled in over 80% of recordings beyond 36 weeks. In contrast, during the first half of the second trimester, recordings were characterized by frequent short bursts of fetal activity which appeared randomly distributed, and the longest periods of complete quiescence were rarely > 5 min. During the second half of the second trimester, the relatively high baseline level of activity was increasingly punctuated by periods of inactivity lasting 6 min or more, so that a cyclical rather than a random distribution of activity became apparent. These cycles of behaviour have been reported previously and referred to as clustering of fetal activities (Sorokin *et al.* 1982), rest and activity cycles (Nasello-Paterson *et al.* 1988) or 'ultradian rhythms' (Campbell 1980). They differ from behavioural states in that linkage of the behavioural state variables, namely eye movements, somatic movements and heart rate pattern is not consistent and as close as in the mature fetus. Because there is no universally agreed definition of 'rest-activity' cycles, for the purpose of this work we arbitrarily defined 'quiet or rest cycles' as occurring when there was continued inactivity for ⩾ 6 min. All fetal breathing episodes lasting at least 5 s and containing at least four consecutive breaths were included and all breath to breath intervals ⩾ 6 s were excluded.

Approval for the study was given by the hospital's research and ethics committee.

Results

Altogether 21 behavioural recordings (3–9 per fetus) lasting a total of 28·3 h were made in the four fetuses with abnormal FVWs, and 268 recordings lasting a total of 402·4 h were made in the 45 low risk fetuses.

Once absence of end-diastolic velocity was observed in the four fetuses, diastolic velocity never returned in the umbilical arteries. Details of these fetuses are summarized in Table 1.

Two fetuses developed low biophysical scores, 3 and 9 weeks respectively after the first abnormal waveform.

Behaviour

When the 6 min quiescence rule was applied to the recordings of the 45 low risk fetuses, the 'rest-activity' cycles were first fulfilled in one recording at 21 weeks, and were present in ⩾80% after 28 weeks. In the four fetuses with abnormal FVWs, five recordings were made before 28 weeks, and in all of these behaviour appeared fairly randomly distributed with periods of inactivity not exceeding 5 min. From 28 weeks 16 recordings were made and all contained 'rest-activity' cycles, and the percentage of time spent in quiescence was similar to that in the low risk fetuses (Fig 1). Behavioural states were present in most recordings of low risk fetuses after 36 weeks, however, only one of the four fetuses with abnormal FVWs was born after 36 weeks, and had well developed apparently normal behavioural states with close linkage of the behavioural state variables and simultaneous change of all three variables at the times of state transition, in the last recording at 35 weeks.

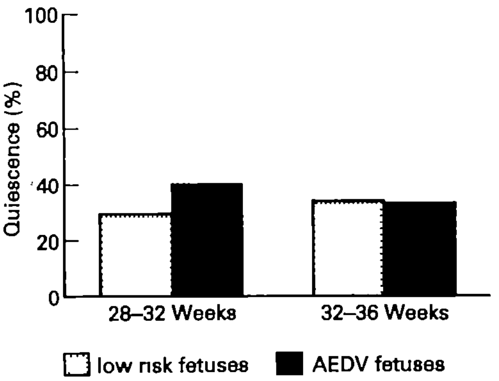

Fig. 1. The mean percentage of time spent in quiescence by the four fetuses with absent umbilical artery end-diastolic velocities (AEDV) and the 45 normally growing fetuses. (28–32 weeks is the mean of 8 recordings in 4 fetuses with AEDV, and 32–36 weeks is the mean of 8 recordings in 2 fetuses with AEDV).

Fetal breathing

The median and centile ranges of the percentage time the 45 low risk fetuses spent breathing is shown in Fig. 2, together with the individual results for the recordings of the four fetuses with abnormal waveforms, all of which fall in the expected range. Similarly, when we looked at the maximum sustained intervals of fetal breathing the values for these four fetuses were all between the 5th and 95th centiles.

Fetal heart rate patterns

In the low risk fetuses the percentage of movements accompanied by fetal heart rate acceleration (defined as a rise in heart rate of ≥ 15 beats/min and sustained for ≥ 15 s), the rate of rise in fetal heart rate (acceleration rate) and height of accelerations showed a significant positive correlation with gestational age (Pillai & James 1990b). The number, rate and height of accelerations in the recordings of the fetuses with abnormal FVWs were smaller than average at comparable gestations, with all values lying between the 5th and 50th centiles.

Fetal outcome

All 45 low risk pregnancies were delivered between 37 and 42 weeks. All 1-min Apgar scores were > 5, and 5-min scores were > 7. The mean birthweight was 3531·9 g (SD 434·9, range 2700–4650). One infant was admitted to the neonatal unit for investigation of pyrexia which settled without treatment, and one other infant died suddenly for unexplained reasons at 8 weeks. All other infants are currently between 1 and 2 years and are developing normally.

Gestation at delivery, Apgar scores and birthweights of the four fetuses with abnormal FVWs are shown in Table 1. All were born by elective caesarean section, with birthweights < 5th centile, and were admitted to the neonatal unit. Cord gases, determined in three of them, were normal. However, in accordance with the policy of the unit, the placentas were left attached and cord clamping was delayed until pulsations had ceased and respiration was established. The effect of this on the cord gases is unknown. The two babies with birthweights < 1000 g were electively intubated at birth, but none required ventilation on the neonatal unit. One infant underwent a hernia repair in the post neonatal period. Currently all are between 1 and 2 years, have shown good 'catch-up' growth and their developmental progress is considered appropriate for their age.

Discussion

Little is known about the effect of acute and chronic insults on the maturation of behaviour in the human fetus, or the time relation between the onset of blood velocity changes and other ultrasound signs of fetal distress. Our data show that the interval between abnormal Doppler findings and the development of an abnormal or equivocal biophysical profile score is unpredict-

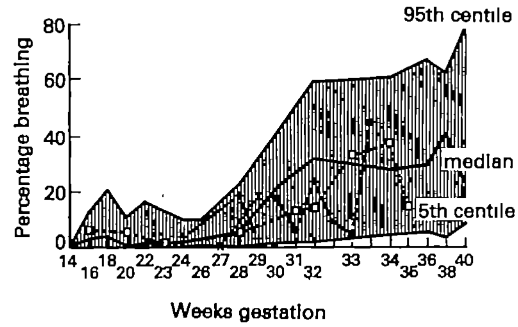

Fig. 2. The 5th–95th centile range for the percentage of time fetuses spend breathing by gestational age for the 45 normally growing fetuses (hatched area), and the percentage values during individual recordings of the four fetuses with absent umbilical artery end-diastolic velocities (AEDV). —×—1, —+—2; —*—3, —□—4.

Table 1. Characteristics of four pregnancies with persistently absent umbilical artery end-diastolic velocities (abnormal FVWs)

Factor	1	2	3	4
Maternal pathology*	PIH	PIH	PIH	Essential hypertension
Duration of abnormal FVWs (weeks)	2	3	7	9
Gestation of delivery (weeks)	29	30	34	36
Indication for delivery†	Maternal	Maternal, low BPS	SGA	SGA, low BPS
Apgar score at				
1 min	8	3	8	5
5 min	10	6	9	7
10 min	–	9	10	10
Birthweight (g)	850	980	1330	1980
Neonatal respiratory support	Intubated	Intubated, headbox $O_2 < 24$ h	Nil	Headbox $O_2 < 6$ h

*PIH, pregnancy-induced hypertension; † Maternal, worsening PIH; BPS, fetal biophysical profile score; SGA, small for gestational age.

able and may be as long as 9 weeks, while a disturbance of neurobehavioural development may not be evident at all. These weeks represent important weeks of maturity, during which intensive fetal behavioural surveillance may compare favourably with neonatal intensive care resources necessary if the infant were born preterm. The appearance of rest activity cycles in the second trimester (Sorokin *et al.* 1982), their lengthening throughout the remainder of pregnancy (Dierker *et al.* 1982b) and emergence of behavioural states around 36–38 weeks gestation (Nijhuis *et al.* 1982) have been described previously. Fetal growth retardation has been associated with a delay in the emergence of behavioural states (van Vliet *et al.* 1985a), due to slower synchronization of the different state variables at the times of state transition, while coincidence of the state variables, the occurrence of the different states (i.e., quiet *vs* active) and fetal breathing were not significantly different to that in low risk fetuses (van Vliet *et al.* 1985b). Thus only a very subtle difference in behaviour has been demonstrated with fetal growth retardation in late pregnancy, and was not evident in our study, since only one of the fetuses with abnormal FVWs was born after 36 weeks gestation and satisfied the criteria for behavioural states.

Studies of sleep state in the fetal lamb have shown that transition from active (REM) to quiet (non-REM) sleep is accompanied by a 30% fall in cerebral oxygen and glucose metabolism (Richardson *et al.* 1985). It may therefore provide a potential protective reflex, and explain why a prolonged period of fetal inactivity and unreactive heart rate is not consistently associated with poor condition at birth. Fetuses of diabetic mothers have a delay in the lengthening of their rest cycles (Dierker *et al.* 1982b) and a delay in the emergence of behavioural states (Bekedam & Visser 1985). It is possible that the occurrence of shorter rest periods may contribute to their susceptibility to sudden unexpected death. In contrast the small fetus associated with chronic uteroplacental disease may be able to survive and be born intact by maintaining the appropriate maturation time-scale of longer rest cycles.

Impaired trophoblastic-maternal interactions have been demonstrated early in the second trimester (Khong *et al.* 1986). However, this is not usually identified as SGA and abnormal FVW until late in the second trimester. Absent umbilical artery end-diastolic velocities have also been shown to predate the development of abnormal fetal heart rate patterns by several weeks (Rochelson *et al.* 1987), and are associated with hypoxia and acidosis (Nicolaides *et al.* 1988), though that report gave no information about the numbers with abnormal fetal heart rate patterns or low biophysical scores.

The data presented support the clinical usefulness of umbilical artery Doppler studies in high risk pregnancies, in that the finding of persistently absent end-diastolic velocities distinguishes a group in whom intensive fetal and maternal surveillance is indicated, for among these fetuses deteriorating maternal condition was the most common indication for delivery. Our data do not support the view that umbilical artery blood flow studies are of value in choosing the optimum time for delivery. It is uncertain whether it is safer for the baby to be born as soon as absent end-diastolic velocities are detected, with the consequences of preterm delivery, or later with the gain of several weeks of gestation. Ultimately these questions posed by the introduction of blood flow studies into obstetrics cannot be answered solely by consideration of fetal behaviour and requirements for neonatal intensive care, but must also take account of long term developmental progress of the infant.

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Perceived risk not actual risk predicts uptake of amniocentesis

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Summary. A consecutive cohort of 71 women eligible for amniocentesis because they were over 38 years of age completed questionnaires during the first trimester of pregnancy. Sixty-one women underwent amniocentesis, an uptake rate of 86%. Uptake was associated with a less negative attitude towards termination of an affected baby and a higher perceived risk of the fetus being abnormal. It was not associated with actual age-related risks. There was no significant relation between actual risk and perceived risk. The results of this study suggests that it is important for doctors to understand the basis of women's decisions to have amniocentesis, and the difference between actual and perceived risk if they are to communicate effectively with women about the test and their options.

Amniocentesis is routinely offered to older pregnant women (i.e., those aged more than 35–38, depending upon the health region) because of the increasing risk of Down's syndrome with age. There is variation in uptake of this procedure, across countries (Reid 1988) and across geographical regions within countries (Edwards 1979). Over the last two decades its use has been increasing (Hunter *et al.* 1987; Knott *et al.* 1986), but relatively few studies have investigated the psychological predictors of uptake (Weinman 1990). Attitudes towards termination and religious beliefs have been found to be associated with hypothetical decisions concerning amniocentesis (Bundey 1978) as well as actual decisions (Bishop 1987). Although eligibility for amniocentesis is based on age-related risk of having a baby with Down's syndrome, there is no evidence to suggest that actual risk is a significant predictor of uptake in older women. We reported previously (Marteau *et al.* 1989) that women who had amniocentesis differed from those who did not in being less concerned about miscarrying the current pregnancy (a risk associated with undergoing amniocentesis) and having a more favourable attitude towards termination of an affected fetus. Perceived and actual age-related risk of having an affected child were unrelated to this decision. There is a general assumption in genetic counselling that counsellees given risk information make reproductive plans that reflect the risk level of the birth abnormality, but recent evidence points to perceived risk as a more important predictor of reproductive intention than actual risk (Shiloh & Saxe 1989).

The aim of this study is to repeat and extend our previous prospective study using a larger sample to determine the extent to which decisions about uptake are influenced by (i)

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knowledge, (ii) actual risk, (iii) perceived risk, (iv) attitudes towards miscarriage, (v) attitudes towards termination of an abnormal baby, and (vi) value attached to having an abnormal child. A further aim is to compare uptake rates for amniocentesis and the factors influencing them before and after a 2-year period in which prenatal diagnosis has become increasingly assimilated into routine antenatal care.

Subjects and methods

All women up to 16 weeks gestation aged 38 or over at the expected date of delivery who presented for antenatal care at a London teaching hospital between September 1987 and August 1988 were eligible for inclusion in the study. Of the 103 such women identified during the study period nine were excluded because they miscarried before the time when amniocentesis would have been carried out; four were not sufficiently fluent in English to complete the questionnaires; nine refused to participate; and ten did not complete both questionnaires. Hence there were 71 full participants.

Measures

Knowledge of prenatal tests. This was assessed using a standardized questionnaire (Marteau *et al* 1988).

Perceived risk of having a baby with an abnormality. This was assessed using an eight-point rating scale, ranging from 0 (not at all likely) to 7 (extremely likely).

Actual risk of having a baby with Down's syndrome. This was taken from the woman's age at the expected date of delivery.

Burden attached to having an abnormal child. This was assessed by asking women how bad it would be for them if they gave birth to a child with a serious abnormality. Responses were made using an eight-point rating scale, ranging from 0 (not at all bad) to 7 (extremely bad).

Attitude towards termination of an affected baby. This was assessed by asking the following question: 'How bad it would be to have a termination because something was wrong with the baby?' Responses were made using an eight-point rating scale, ranging from 0 (not at all bad) to 7 (extremely bad).

Attitudes towards miscarriage of the current pregnancy. This was assessed by asking women to rate how bad it would be to lose the current pregnancy through miscarriage. Responses were made using an eight-point rating scale, labelled at one end, 'not at all bad' (0), and at the other end, 'extremely bad' (7).

Anxiety. State and trait anxiety were measured using the Spielberger State-Trait Anxiety Inventory (Spielberger *et al.* 1970).

Demographic and obstetric history. Information concerning women's ages at the expected date of delivery, socio-economic status, ethnic origin, previous pregnancies and uptake of amniocentesis were taken from women's medical notes.

Procedure

Women routinely attend the hospital antenatal clinic on two occasions before the time when

Table 1. Factors associated with uptake of amniocentesis in 71 women

Factor	Amniocentesis (n = 61)	No amniocentesis (n = 10)
Knowledge of tests used		
First visit	4·9 (1·3)	4·7 (1·8)
Second visit	5·5 (0·8)	5·4 (0·7)
Perceived risk of affected fetus	2·5 (1·7)	1·3 (0·9)*
Burden of affected child (how bad)	6·5 (1·0)	6·5 (0·7)
Attitude to miscarriage (how bad)	5·5 (1·8)	5·6 (1·4)
Attitude to termination (how bad)	5·1 (2·3)	6·7 (0·5)†
Anxiety		
Trait	40·3 (7·9)	37·5 (10·2)
State	39·7 (10·1)	37·8 (8·9)

Results are mean (SD) values of scores (see text).
* $P<0·01$; † $P<0·0001$ (t-tests).

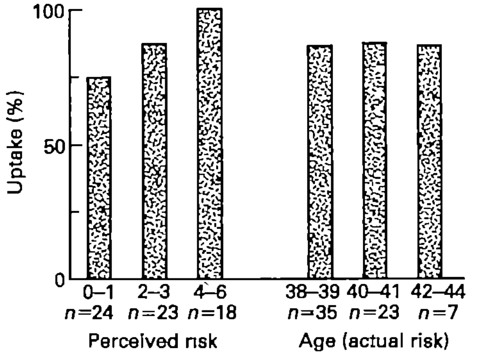

Fig. 1. Relation between uptake of amniocentesis and perceived risk scored from 0 (not at all likely) to 7 (extremely likely); and between uptake and actual risk (based on maternal age) in 65 women.

amniocentesis could take place. At the first clinic visit at between 12 and 14 weeks gestation, the women see a midwife and various tests are offered, including amniocentesis. Women return to see an obstetrician one week later. Amniocentesis is performed at between 16 and 18 weeks gestation. Women in the study completed the knowledge and anxiety questionnaires at the first clinic visit, before seeing the midwife; at their second clinic visit they completed the knowledge questionnaire (for a second time) and the perceived risk, value and attitude scales, before seeing the obstetrician.

Results

Of the 71 full study participants 61 had an amniocentesis, an uptake rate of 86%. There was no difference in uptake rate between full study participants and those who refused to participate, were not fluent in English or for whom there was missing data ($\chi^2 = 3{\cdot}58$; df = 1; ns). Women who underwent amniocentesis differed from those who did not in holding less negative attitudes towards termination of an affected baby and a higher perceived risk of the fetus being abnormal (Table 1).

They did not differ in their knowledge about prenatal tests, perceived burden of having an abnormal child, attitude towards miscarriage, state or trait anxiety, obstetric history, socioeconomic status, ethnicity or age and, by inference, risk of having a child with Down's syndrome. There was no significant relation between actual risk (taking age as an index) and perceived risk ($r = 0{\cdot}10$). This was true for those undergoing amniocentesis and those not having it (Fig. 1)

To compare the results of the current study with those of the previous study (Marteau *et al.* 1989), scores on the four variables that discriminated in either study between those having amniocentesis and those that did not are presented in Table 2.

The uptake rate of amniocentesis was significantly lower in the 1986 study group (56%) than in the 1988 group (86%) ($\chi^2 = 8{\cdot}37$; df = 1; $P<0{\cdot}01$). These rates reflect the hospital rates for these 2 years (58% and 84% respectively). The two groups differed in their attitudes towards termination of an affected child and having a miscarriage: women in the 1986 study had significantly more negative attitudes towards termination of an affected child and more negative attitudes towards losing their current pregnancy through a miscarriage, than women in the 1988 study. The groups did not differ in perceived risk or burden attached to having an abnormal child.

Discussion

Women's decisions concerning amniocentesis were related to their attitudes towards termination of an affected baby and perceived risk of an abnormal fetus. Actual risk of having a child

Table 2. Attitudes of women in 1986 and 1988 who were eligible for amniocentesis on the basis of maternal age

	1986 (*n* = 18)	1988 (*n* = 71)
Attitude towards termination of an affected child (how bad)	6·4 (1·0)	5·3 (2·2)*
Attitude towards miscarriage (how bad)	6·3 (0·9)	5·5 (1·7)*
Perceived risk of having an abnormal child (how bad)	1·7 (1·5)	1·9 (1·6)
Burden attached to having an abnormal child (how bad)	6·8 (0·6)	6·5 (0·9)

Results are mean (SD) scores on 8-point rating scales ranging from 0 (not at all) to 7 (extremely)
* $P<0{\cdot}01$ (*t*-tests).

with Down's syndrome did not influence their decisions. There was no relation between age-related risk of Down's syndrome and perceived risk. These last two negative findings are particularly striking. When obstetricians discuss amniocentesis with women, the probability of having a child with Down's syndrome is invariably presented (Marteau *et al.* unpublished observations). It is a belief commonly held by medical and nursing staff that an 'informed decision' to have amniocentesis is one based on actual risk figures. There are several possible reasons why perceived and actual risk were unrelated. First, it may be that these women did not know their true risks, hence the discordance between true risk and perceived risk. Whilst risk information is invariably given to women, perceived risk was measured before women saw the obstetrician. Alternatively, they may have known their true risk, but varied in how they perceived these figures. It is possible that people do not make fine discriminations between risks of 1:200 and 1:100 whereas they perceive differences between 1:4 and 1:100. It is also possible that women do not perceive their risk as being on a scale but, in focusing upon possible outcomes, translate risk information into either a 50–50 chance (Carter *et al.* 1971) or binary form—it either will or will not happen (Lippman-Hand & Clarke Fraser 1979).

This study raises the question of why the uptake rate has increased from 56% in 1986 to 86% in 1988. Given world-wide reports of increasing use of this procedure over the last 15 years (Knott *et al.* 1986; Baird *et al.* 1985; Fergusson-Smith 1983), it is unlikely that our results are due to chance.

There are several possible sources of change: social influences, pregnant women and their families, and doctors. Concerning social influences, perhaps amniocentesis has become more acceptable as its use increases, thus the increase in uptake is the continuation of a pre-existing trend. The increased use may in part reflect an increasing intolerance of disability, an intolerance that some have argued is fostered by the widespread availability of prenatal screening for fetal abnormality (Stacey 1988). Comparison between the perceived burden of an abnormal child in 1986 and in the current study do not support this argument. Farrant (1985) argues that women's anxiety about fetal abnormality are reinforced by current health and social policies which have the effect of exacerbating women's feelings of personal responsibility for the health of their babies and of placing the burden of responsibility for care upon women's shoulders. The difference in attitudes towards termination of an affected fetus between women in 1986 and 1988 might be a reflection of such an influence. Alternatively, changes in attitudes to termination may stem from wider discussion of abortion. The 2-year period in question includes the debate surrounding 'The Alton Bill' in which arguments for the rights of women to terminate a pregnancy if fetal abnormalities were detected were publicised in the media.

The increased use may be part of a more general phenomenon described by Tymstra (1989) as the imperative nature of medical technology, such that patients appear to attach considerable value to the offer of a screening test, and participate in order to avoid regret at not having done so.

Second, pregnant women are perhaps increasingly reluctant to accept uncertainty concerning the outcome of their pregnancies. Enkin & Chalmers (1982) suggest that the marked improvements in pregnancy outcomes since the Second World War have encouraged expectations to rise even faster than achievements The complexity and pervasiveness of the screening procedures that characterize antenatal care today, they argue, are manifestations of our unwillingness to tolerate these uncertainties. Rothman (1986) argues that the mere existence of prenatal screening raises women's awareness of the likelihood of fetal abnormality thereby increasing their demand for screening. The increase in women's perceived risk of having a baby with an abnormality between 1986 and 1988 is not significant and thus does not support this hypothesis. Alternatively, increasing use of prenatal screening may reflect more liberal attitudes towards abortion of abnormal fetuses. Comparison of attitudes towards termination in the 1986 study cohort with those of the 1988 cohort supports this hypothesis. It is equally possible, however, that this change in attitude may follow an increase in uptake of amniocentesis.

Third, the increase in uptake may represent a change in doctors' attitudes and behaviour towards these tests. Crandall *et al.* (1986), for example, argue that amniocentesis should be made available to all women aged 30 or more. Evidence of an enthusiastic approach by doctors to this test was obtained from tape recordings of routine consultations between obstetricians and women aged over 38. Amniocentesis was presented in a very favourable light and as 'the sensible thing to do'. Two women in the study declined the test: the doctors spent some time attempting to dissuade them, in one instance using incorrect risk figures to do so (unpublished observations). One reason why doctors may be trying to ensure a high uptake of amniocentesis is a fear of litigation. In the health region in which the study took place a woman who was not offered amniocentesis tried to sue the Health Authority following the birth of her child with Down's syndrome. The case was settled out of court. Doctors may feel that they can reduce the likelihood of litigation by erring on the side of encouraging patients to undergo tests. A further factor that may be influencing doctors' positive attitudes towards amniocentesis is suggested by Farrant (1985), who argues that technology enhances the status of obstetrics as a specialty and enables the medical profession to maintain their position as 'key players' in antenatal care.

In sum, these results show that uptake of amniocentesis is influenced by attitudes towards termination of an affected pregnancy as well as perceived risk of having an abnormal child; age-related risk was not associated with this decision. It is important that doctors understand the basis of women's decisions to have amniocentesis and the difference between actual and perceived risk if they are to communicate effectively with women about the test and their options.

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Fetal liver dysfunction in Rh alloimmunization

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Summary. The liver enzymes, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP), were measured in the blood of 25 fetuses with severe Rh alloimmunization at the time of their first, second and third intravascular transfusions and in 17 comparison fetuses. In the comparison group, GGT increased with advancing gestation ($r = 0{\cdot}7$; $P = 0{\cdot}002$), whereas ALP, AST and ALT did not correlate with gestational age. Rh hydropic fetuses ($n = 8$) had higher blood ALT levels than the comparison fetuses ($P = 0{\cdot}008$) and significantly increased transaminases when compared with non hydropic fetuses ($n = 17$). In hydropic fetuses, AST correlated with the nucleated red cell count before transfusion ($r = 0{\cdot}94$; $P = <0{\cdot}0001$). Fetal transaminases were no longer increased in hydropic fetuses by the second (AST) or third (ALT) transfusion. In both hydropic and non hydropic fetuses, GGT increased by the second transfusion (median percentage change +85%, range −83% to +596%; $P = 0{\cdot}003$). The rise in fetal GGT was transitory and correlated with the increase in fetal haematocrit at the first transfusion ($r = 0{\cdot}58$; $P = 0{\cdot}006$). This study reports liver dysfunction secondary to extramedullary erythropoiesis in Rh alloimmunization and implicates portal hypertension for the rise in fetal GGT with transfusion.

Despite recent advances in the treatment of fetal anaemia, hydrops secondary to feto-maternal alloimmunization is still significantly associated with adverse outcome.

Hydrops is not usually manifest until the fetal haemoglobin (Hb) falls more than 7 g/dl below the mean for gestational age (Nicolaides *et al* 1988) or, in the second trimester, until the haematocrit (Hct) is <15% (Nicolaides *et al.* 1985a). The excess of perinatal losses in hydropic fetuses might be attributed to a higher procedure-related complications rate, given that more anaemic fetuses require transfusions of greater volumes which thus take longer to perform. However, review of reports published between 1986 and 1989 indicates that survival after reversal of hydrops (38 of 42, 90%) is significantly better than in fetuses with persistent hydrops after intravascular transfusion (10 of 24, 42%) (P<0·001) (Berkowitz *et al.* 1986; Nicolaides *et al.* 1986; McKenzie *et al.* 1987; Socol *et al.* 1987; Westgren *et al.* 1988; Parer 1988; Har-

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man *et al.* 1988; Grannum *et al.* 1988). These findings suggest that the pathological changes associated with hydrops, rather than anaemia, may predispose to perinatal loss.

Although the pathophysiology of hydrops is poorly understood, fetal hypoxaemia, cardiac and liver dysfunction (Nicolaides *et al.* 1985b; Grannum *et al.* 1988) have all been suggested as mechanisms. Liver involvement is implicated by the common findings of fetal hypoproteinaemia (Nicolaides *et al.* 1985b) and liver enlargement (Roberts *et al.* 1989), both presumably due to parenchymal infiltration with erythropoietic tissue, which in turn might lead to portal hypertension.

We have reported previously that the rise in umbilical venous pressure which occurs with intravascular transfusion is directly related to the rise in fetal Hct (Nicolini *et al.* 1989). The effect on liver function of a parallel increase in portal vein pressure has not been investigated.

The aim of this study was to determine the degree of impairment of liver function in fetal anaemia, especially in hydropic fetuses, and its evolution following intrauterine transfusion.

Subjects and methods

Liver enzymes were measured serially in fetuses with severe Rh alloimmunization at the time of their first ($n = 25$), second ($n = 19$) and third ($n = 22$) intravascular transfusion. Seventeen fetuses undergoing blood sampling for prenatal diagnosis of haematological disorders or rapid karyotyping and later found to be unaffected were selected as a comparison group.

Fetal blood sampling and transfusion were performed under ultrasonic guidance using a 20 gauge needle, as described elsewhere (Nicolini *et al.* 1988a). The site of sampling/transfusion was the umbilical vein either at the placental cord insertion or at its intrahepatic portion (Nicolini *et al.* 1988b). Before and after completion of each transfusion, 2 ml of fetal blood were collected for immediate determination of Hct and acid-base balance (Nicolini *et al.* 1988) and for subsequent nucleated red cell (NRC) count (Fisk *et al.* 1989).

In the comparison group mean gestational age was 23·5 weeks (SD 4·3, range 18–32). In Rh fetuses, the mean gestational age at first transfusion was similar being 23·4 weeks (SD 3·7; range 18–32) and mean initial fetal Hct was 18·6% (SD 7·9, range 6–31).

Seventeen of the 25 Rh fetuses had no signs of hydrops (group 1), while the remaining eight had varying degrees of ascites and/or subcutaneous oedema (group 2). The mean gestational age in group 1 was slightly higher than in group 2 ($P = 0{\cdot}06$), while initial fetal Hct in the hydropic fetuses was significantly lower than in the non hydropic fetuses ($P<0{\cdot}0001$) (Table 1).

Rh negative donor blood, packed to a Hct of 60–80%, was transfused intravascularly to achieve a final Hct in the vicinity of 40% (Nicolaides *et al.* 1986). Mean fetal Hct after transfusion was 43·7% (SD 6·5, range 31–59) with no significant difference between hydropic and non hydropic fetuses (Table 1).

No immediate complications occurred and the second intrauterine transfusion was given 2–5 weeks after the first (non hydropic group: median 3, range 2–5; hydropic group : median 2, range 1–4; $P = 0{\cdot}23$). No significant difference was found between the two groups in fetal Hct at the second and third transfusions (Table 1). Hydrops resolved in three of the eight hydropic fetuses. In no case was fetal acidaemia or hypoxaemia, found either before or after transfusions (Nicolini *et al.* 1988a).

NRC count was lower in the non hydropic than in the hydropic fetuses before the first transfusion, but the difference was no longer apparent at the second transfusion (Table 1).

A 1 ml sample of fetal blood obtained before, and immediately after, the first transfusion and before the second and third transfusions, was assayed for aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) at 37°C using a Coulter CPA (Coulter Electronics Ltd, Luton, UK). Coefficients of variation were 2% and 4% at high and low activity levels respectively.

Paired or unpaired Student's *t*-tests were used for statistical assessment, as appropriate, if a normal distribution was confirmed on histograms. Otherwise, the non-parametric Wilcoxon or Mann–Whitney *U* tests were used.

Results

In the comparison group, fetal AST, ALT and ALP did not correlate with gestational age, whereas GGT increased significantly with advancing gestational ($r = 0{\cdot}7$; $P = 0{\cdot}002$). Mean fetal GGT increased from 38·8 IU/l at 18 weeks to 98·5 IU/l at 36 weeks gestation. Fetal

Table 1. Haematological data at fetal blood sampling in Rh fetuses with or without fetal hydrops

	Non hydropic fetuses				Hydropic fetuses		
Variable	Mean	(SD)	Range	*P*	Mean	(SD)	Range
Before 1st transfusion		(*n* = 17)				(*n* = 8)	
GA	24·3	(3·8)	19–32	ns	21·6	(2·7)	18–25
Hct	22·3	(6·4)	12–31	0·0001	10·5	(3·5)	6–16
NRC	3·4*		0·3–33	0·02	26·0*		2–85
After 1st transfusion							
Hct	43·7	(7·9)	33–59	ns	43·6	(6·1)	31–56
Before 2nd transfusion		(*n* = 13)				(*n* = 6)	
GA	27·1	(3·9)	22–34	0·02	23·4	(2·6)	20–27
Hct	22·6	(6·7)	9–34	ns	26·4	(3·9)	21–31
NRC	0·3*		0–22	ns	0*		0–3
Before 3rd transfusion		(*n* = 15)				(*n* = 7)	
GA	29·2	(3·4)	25–34	ns	26·3	(3·5)	23–30
Hct	28·6	(7·3)	14–43	ns	28·7	(6·1)	22–34

* Median

GA = gestational age (weeks). Hct = haematocrit (%). NRC = nucleated red cell count (× 10^9/l).

AST, ALT and ALP showed a non parametric distribution both in controls and Rh fetuses.

Before the first transfusion, Rh fetuses, overall, had blood levels of liver enzymes similar to those in the comparison group. However, hydropic fetuses had a significant increase in ALT ($P = 0{\cdot}008$) and, when compared with non hydropic fetuses, had significantly higher AST and ALT, whereas ALP and GGT were similar (Table 2).

In hydropic fetuses, AST was significantly correlated with the NRC count before transfusion ($r = 0{\cdot}94$; $P < 0{\cdot}0001$). Multiple regression analysis showed that this association was independent of gestational age and initial fetal Hct ($P < 0{\cdot}03$). The correlation with the NRC count was confirmed in both hydropic and non hydropic fetuses in whom AST values were above the reference range of 42 IU/l (maximum observed value in the comparison group) (Fig. 1).

There was no significant change in any of the liver enzymes at the end of the first transfusion.

In hydropic fetuses, ALT blood levels remained higher than in the comparison group (median 2·0 IU/l, range 1–9; $P = 0{\cdot}01$) at the second transfusion, but were similar at the third (median 0 IU/l; range 0–4). Fetal AST had become similar in hydropic (median 21·5 IU/l; range 5–29) and non hydropic fetuses (median 16 IU/l, range 4–47) by the second transfusion.

Overall, there was a statistically significant ($P = 0{\cdot}003$) increase in fetal GGT by the second transfusion and 64% of Rh fetuses had values above the reference range (Fig. 2). However, before the third transfusion fetal GGT was no

Table 2. Medians and ranges of blood levels of liver enzymes in the comparison group and in the Rh fetuses at the first transfusion

	n	ALT	AST	ALP	GGT
Comparison group	17	0 (0–6)	20 (9–42)	173 (89–213)	62 (31–108)
Non hydropic group	17	0* (0–5)	12† (3–64)	162 (97–234)	66 (22–411)
Hydropic group	8	3‡ (0–9)	49 (9–97)	139 (26–210)	97 (23–271)

Significance of differences: Non hydropic *vs* hydropic group * $P = 0{\cdot}007$; † $P = 0{\cdot}02$; Hydropic *vs* comparison group ‡ $P = 0{\cdot}008$.

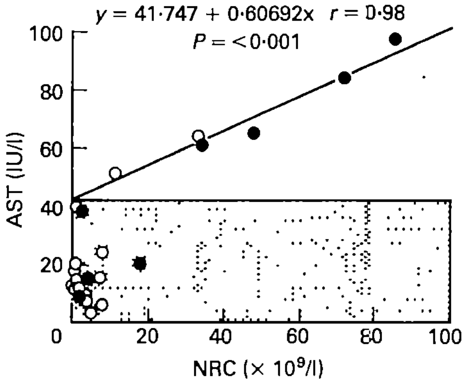

Fig. 1. Correlation between nucleated red cell count (NRC) and aspartate transaminase (AST) at the initial blood sampling in fetuses with AST values above the reference range. Closed circles = hydropic fetuses, open circles = non hydropic fetuses.

longer statistically increased compared to basal values (Fig. 3). The median percentage rise in GGT at fetal blood sampling 2–5 weeks after the first transfusion was +85% (range −83% to +596%) and correlated with both the initial fetal NRC count ($r = 0{\cdot}45$; $P = 0{\cdot}04$) and with the increase in fetal Hct during the first transfusion ($r = 0{\cdot}58$; $P = 0{\cdot}006$) (Fig. 4). Although the increase in GGT at the second transfusion was statistically significant for both groups (non hydropic: median +61%, $P = 0{\cdot}01$; hydropic: median +352%, $P = 0{\cdot}02$), the correlation with the rise in fetal Hct was only significant in the hydropic group ($r = 0{\cdot}66$). The largest percentage change (+596%) was observed in a fetus in which signs of hydrops had disappeared by the time of the second transfusion.

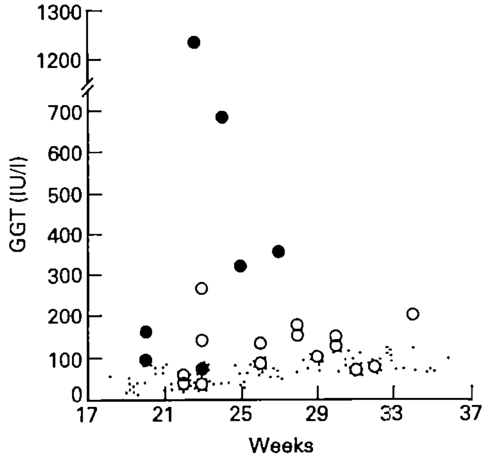

Fig. 2. Blood levels of γ-glutamyl transpeptidase (GGT) in Rh fetuses at the second transfusion. Closed circles = hydropic fetuses; open circles = non hydropic fetuses; shaded area = comparison fetuses.

Discussion

This study shows that fetuses with hydrops due to Rh alloimmunization, when compared to non hydropic fetuses, have significant elevation of fetal transaminases before the first transfusion. However, there was considerable overlap between hydropic and non hydropic fetuses and in both groups elevation of NRC count was associated with a rise in AST. This suggests that liver infiltration, rather than hydrops itself, leads to liver dysfunction. NRC counts reflect the degree of extramedullary erythropoiesis and have been shown to be correlated with the fetal Hb deficit (Nicolaides *et al.* 1988). Therefore, liver infiltration by erythropoietic tissue may be assumed in the presence of a high NRC count. The observed rise in fetal AST with increasing NRC counts can be explained by hepatocellular damage, which, in the adult, is indicated by elevation of blood levels of AST and ALT (De Ritis 1972). Alternatively, decreased transaminase clearance might be a mechanism, since both enzymes are catabolyzed by the reticulo-endothelial system, especially within the hepatic sinusoids (Kasimoto *et al.* 1985). This latter hypothesis is supported by our finding that the remaining indices of liver function, GGT and ALP, were not increased with hydrops before transfusion.

Hydrops has been suggested as being due to the combined effect of portal hypertension and

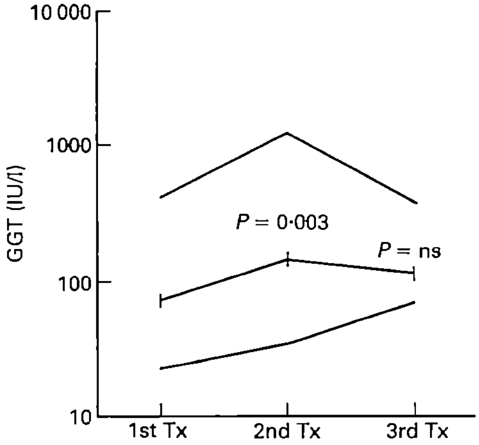

Fig. 3. Changes in medians and ranges of fetal γ-glutamyl transpeptidase (GGT) with transfusions: (Tx)· log scale.

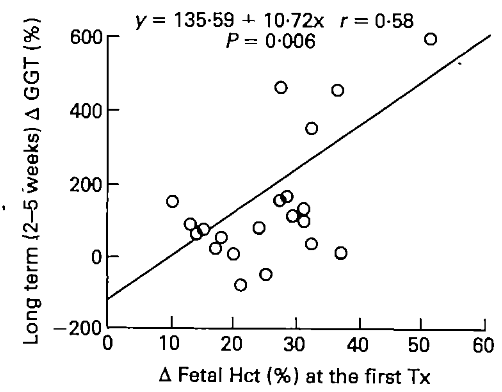

Fig. 4. Correlation between the percentage change in fetal γ-glutamyl transpeptidase (GGT) (prior to the 2nd transfusion—pre 1st transfusion/pre 1st transfusion × 100) and the percent increase in fetal hematocrit (Hct) during the 1st transfusion.

hypoproteinaemia. While the former has never been demonstrated, the latter has been found not only in hydropic, but also in 60% of non hydropic, but severely anaemic, fetuses (Nicolaides *et al.* 1985b).

Similarly, liver dysfunction, although more common in hydrops, is not specific to it, but instead seems a consequence of fetal anaemia. Indeed, following correction of fetal anaemia by intravascular transfusion and normalization of the NRC count, a progressive decrease in fetal transaminases was observed.

In contrast, intrauterine transfusion produced a significant increase in fetal GGT, which was more marked in hydropic fetuses. Intrauterine growth retardation and fetal hypoxaemia have been reported to be associated with elevation of fetal GGT (Cox *et al.* 1988; Bartnicki *et al.* 1989). Since the blood oxygen content and fetal $P\mathrm{o}_2$ are reduced when Hb is <4g/dl (Soothill *et al.* 1987), high baseline values of GGT might be expected in the presence of anaemia. This was not the case, as GGT before the first transfusion was similar to controls, even in hydropic fetuses. Furthermore, normalization of the blood oxygen content follows correction of fetal anemia.

Fetal iron storage, as expressed by blood ferritin levels, increases proportionally with the number of transfusions and the cumulative volume of blood transfused (Nasrat *et al.* 1991). This rise in fetal GGT therefore might be explained by liver dysfunction secondary to extensive iron deposition which can be demonstrated histologically in Rh fetuses having undergone serial intrauterine transfusions. According to this hypothesis, however, GGT should rise progressively with increasing order of transfusion. The observed trend suggests, instead, that the increase in GGT is transitory and specific to the first transfusion, when the relative amount of transfused blood is largest in order to correct fetal anaemia.

We have previously reported that long term changes in liver enzymes levels with transfusion are unrelated to the site of sampling (Nicolini *et al.* 1990). However, a small immediate increase in fetal GGT occurs when the transfusion is performed at the intrahepatic vein (Nicolini *et al.* 1990). This finding could be due to a higher rise in portal pressure due to blood volume expansion. Although no significant differences in blood volume between hydropic and non hydropic fetuses have been reported (Nicolaïdes *et al.* 1987), a considerable increase in blood volume is produced by intravascular transfusion. As the rise in umbilical vein pressure is proportional to the relative amount of blood transfused, as indicated by the increase in fetal Hct (Nicolini *et al.* 1989), we suggest that portal hypertension may have accounted for the observed changes in fetal GGT which were greater in hydropic fetuses and which correlated significantly with the increase in fetal haematocrit at the first transfusion. Similarly, an increase in portal hypertension may be responsible for the temporary deterioration of fetal hydrops which we have occasionally observed following transfusion.

Fetal GGT is elevated in intrauterine infection (Daffos *et al.* 1988), which may also lead to hydrops, raising the possibility that GGT may be a non specific marker of disorder in the hepatic circulation.

Although ALP, in the adult, appears to be raised in the same spectrum of hepatobiliary disease as GGT is, fetal ALP did not change with transfusion. We did not test the heat stability of the measured ALP, but previous studies have shown minimal passage of placental ALP into the fetal circulation (Shane & Suzuki 1974). On the other hand, ALP derived from bone osteoblasts might account for the high levels detected in the fetus compared to adults, which in turn might have masked any changes in its liver isoenzyme.

This study demonstrates liver dysfunction secondary to extramedullary erythropoiesis in anaemic Rh alloimmunized fetuses. Whereas transaminases revert to normal with correction of fetal anaemia, a marked rise in fetal GGT occurs in an opposite fashion after the first transfusion and is directly correlated to the amount of blood transfused.

These findings should prompt long term follow-up of liver function in newborns who underwent intrauterine treatment for Rh alloimmunization.

Acknowledgments

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Oestrogen and androgen states in oligo-amenorrhoeic women with polycystic ovaries

R. FOX, E. CORRIGAN, P. G. THOMAS, M. G. R. HULL

Summary. Oestrogen and androgen states have been studied in relation to ovarian morphology defined by ultrasonography in 65 women with oligo-amenorrhoea. Of the 48 women with polycystic ovaries (PCO), 44 (92%) had a withdrawal bleed following progestogen challenge (indicating oestrogenization) compared with just three (18%) of the 17 with non-PCO ($P<0{\cdot}001$). Median serum concentrations of oestradiol and oestrone were statistically significantly higher in the PCO group but the ranges overlapped widely. Of the four women with PCO but oestrogen deficiency, two were hirsute and had evidence of a severe form of the disorder. The other two were not hirsute and appeared to have hypothalamic dysfunction associated with weight loss overriding the disorder due to pre-existing PCO. Compared with the non-PCO group, the PCO subgroup without hirsutism ($n = 31$) had statistically significantly higher median values of LH, testosterone, androstendione, and dehydroepiandrosterone sulphate concentrations, and free androgen index. Concentrations of androgen, but not LH, were significantly higher still in the PCO subgroup with hirsutism ($n = 17$).

Evidence of oestrogenization in polycystic ovarian disease is not a new observation (Leventhal 1958) but it has not been widely recognized or studied adequately. Kletsky *et al.* (1975) suggested that menstrual bleeding following progestogen challenge together with a raised LH level was indicative of polycystic ovarian disease (PCOD). Hull (1987) demonstrated close similarities in the hormonal findings, particularly for LH levels, between hirsute women with presumed PCOD and oestrogenized non-hirsute women with oligo-amenorrhoea, but in non-hirsute oestrogen-deficient women, most of whom had amenorrhoea associated with weight loss or hyperprolactinaemia, the hormonal findings were quite different. Deducing that oestrogenization alone was sufficient evidence to presume PCOD, Hull (1987) calculated that PCOD was present in 37% of women with amenorrhoea and in 90% with oligomenorrhoea, rates similar to those found by Adams *et al.* (1986) using ultrasonography (26% and 87% respectively). However, in the studies by Kletsky *et al.* (1975) and Hull (1987), the diagnosis of PCOD was presumed, and oestrogen state and ovarian morphology have yet to be compared directly.

The aims of this study were to test the hypothesis that oestrogenization (of the endometrium)

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is a key feature of oligo-amenorrhoeic women with polycystic ovaries (PCO), and to compare the serum hormone concentrations in subgroups with and without hirsutism, using ultrasonography to define ovarian morphology.

Patients and methods

A consecutive series of 65 women presenting to the Reproductive Medicine Clinic at the Bristol General Hospital with functional oligomenorrhoea (menstrual intervals >6 weeks) or amenorrhoea (no menstrual loss for ≥ 6 months) was studied prospectively. Functional oligo-amenorrhoea was defined by exclusion of readily identifiable causes such as primary hypothalamic, pituitary and ovarian failure, ovarian and adrenal androgen-secreting tumours, hyperprolactinaemia, thyroid and other extra-ovarian endocrine disorders, uterine abnormalities and pregnancy.

All women underwent ultrasonography and started endocrine testing simultaneously. The ultrasound examinations were all made by the same investigator (R.F.) using an Ausonics MicroImager 1000 with a 3.5 MHz long-focus abdominal transducer and a 7·5 MHz short-focus vaginal endoprobe. Wherever possible the vaginal method was used for greater clarity. Patients were classified as having polycystic ovaries (PCO) or not (non-PCO). The distinction between normal, inactive and multifollicular ovarian types is not made for the purposes of this study. The criteria for diagnosing PCO with vaginal ultrasound were modified from those established by Adams *et al.* (1985), who had used an abdominal transducer, because a greater number of the smaller cysts can be seen using a vaginal probe: at least 15 cysts (median >20) of 2–10mm diameter per ovary usually arranged around the ovarian cortex and a prominent, highly echogenic stromal compartment. In non-PCO there were fewer than 12 such cysts per ovary (median six) and minimal stroma (Fox & Hull unpublished data). An additional four women had been excluded because of inadequate inspection of the ovaries during ultrasonography (6%).

Hair growth was assessed clinically using an adaptation of the scoring system described by Ferriman & Gallwey (1961), taking an equivalent of their 'hormonal' score of ≥12 to indicate unequivocal hirsutism. This stringent criterion was adopted for the purpose of this study in order to distinguish true hirsutism from minor degrees of male pattern hair growth which are common within the general population (Rittmaster & Loriaux, 1988).

Oestrogen state was determined by a progestogen challenge test (oral medroxyprogesterone acetate (Provera, Upjohn) 5 mg daily for 5 days) to induce menstrual bleeding in the ensuing week. Normal menstrual loss indicates oestrogenization (of the endometrium) and absent, or occasionally scanty, loss indicates oestrogen deficiency (Hull *et al.* 1979; Shulman *et al.* 1989).

Serum LH and FSH concentrations were determined by specific radioimmunoassays (RIA) using polyclonal rabbit antisera (WRB/F87 for LH and M93/6873 for FSH; Pharmacia Diagnostics) standardized against international reference preparations. Following ether extraction, testosterone and androstenedione were measured by specific RIA using polyclonal antisera (HP/5/55/–1A sheep antiserum, University of Surrey, Guildford for testosterone and rabbit antiserum, Women's Hospital, Birmingham for androstenedione). Dehydroepiandrosterone sulphate (DHEAS) was assayed using a competitive non-extraction RIA using a polyclonal sheep antiserum (St Thomas's Hospital, London). 17β-oestradiol (E_2) was estimated by a competitive non-extraction RIA using an ER-155 kit (Baxter Health Care), and, following extraction by diethyl-ether, oestrone (E_1) was measured by a specific RIA using a polyclonal antiserum from rabbit (University College, London). Sex hormone-binding globulin (SHBG) concentrations were determined by non-competitive immunoradiometric assay (IRMA) using ^{125}I-labelled anti-SHBG mouse monoclonal antibody (Farmos Diagnostica). Inter-assay coefficients of variation for the hormone assays ranged from 7% to 10%. The free androgen index (FAI) was calculated using the formula:

$$\text{Testosterone (nmol/l)} \times 100 \,/\, \text{SHBG (nmol/l)}$$

The hormonal results were compared between patients classified according to the ultrasound appearances of the ovary (PCO *vs.* non-PCO). The data are expressed as medians and ranges, and compared using the Mann–Whitney *U*-test. Proportions were compared using the χ^2 test with Yates' correction. Significance was taken as $P \leq 0{\cdot}05$.

This study was approved by the ethics committee of the Bristol and Weston Health Authority.

Results

Of the 65 patients studied, 44 had oligomenorrhoea and 21 had amenorrhoea. Of the oligomenorrhoeic women 40 (91%) had PCO compared with eight (38%) of those with amenorrhoea. Of the 48 patients with PCO, 17 (35%) were hirsute but none of the non-PCO group had abnormal hair growth ($\chi^2 = 6{\cdot}42$, $P<0{\cdot}01$).

Table 1 gives the endocrine findings for the patients with PCO, divided according to the presence or absence of hirsutism, and for those with non-PCO. All of the patients with PCO had at least one abnormal biochemical feature, either a high LH (>10·0 U/l) concentration, elevated LH:FSH ratio (>2·5) or raised FAI (>4·5) compared with just two (12%) of the non-PCO patients ($\chi^2 = 50{\cdot}2$, $P<0{\cdot}001$). Four (8%) of the PCO group, but none of the non-PCO group, had evidence of abnormal adrenal androgen production (greater than DHEAS concentrations 11·5 μmol/l).

Of the 48 patients with PCO, 44 (92%) were oestrogenized compared with three (18%) of the non-PCO group ($\chi^2 = 30{\cdot}75$, $P<0{\cdot}001$). The four exceptions of PCO with oestrogen deficiency are worthy of more detailed description. Two were androgenized, both severely so, and had total testosterone concentrations of >5 nmol/l together with raised DHEAS values indicating adrenal androgen hypersecretion. The other two women, who were non-hirsute, presented with amenorrhoea related to a clear history of weight loss and stress. These features were assumed to be the cause of their anovulation, overriding any pre-existing disorder due to PCO as manifested by previously erratic menstruation. At the time of study these two women had normal levels of LH, FSH, testosterone and androstenedione, but moderately elevated free testosterone levels due to reduced concentrations of SHBG. Attempts to induce ovulation in one led to tonically raised LH levels but without the development of a dominant follicle

Of the three women with non-PCO and evidence of oestrogenization, one had borderline elevation of FSH levels suggestive of atypical ovarian failure, the second had Turner's mosaicism (XX/XO) but without ovarian failure, and the third was tested during recovery from weight loss-related amenorrhoea.

Discussion

Interpretation of the results of this study depends on the accuracy of the ultrasound diagnosis of PCO. A recent study by Saxton *et al.* (1990) has verified the ultrasound diagnosis of PCO histologically but studies comparing ultrasonography with magnetic resonance imaging indicate that a diagnosis of non-PCO with an abdominal ultrasound probe is less reliable because of its inability to display small follicles in obese patients (Mitchell *et al.* 1986; Faure *et al.* 1989) By using a vaginal transducer, we were able to overcome the problems of transabdominal ultrasonography.

The results show strong association between oestrogen state and ovarian morphology, confirming our hypothesis that oestrogenization is a key feature of PCO, in contrast to other causes of functional oligo-amenorrhoea. Our findings include amenorrhoeic women with PCO, most of whom were also oestrogenized. The progestogen challenge test therefore constitutes a simple method of distinguishing between the dif-

Table 1. Hormonal concentrations in oligo-amenorrhoeic women with and without polycystic ovaries (PCO)

	PCO						Significance of difference*			
	Hirsute (*n* = 17) (a)		Non-hirsute (*n* = 31) (b)		Non-PCO (*n* = 17) (c)		(a) *vs* (b)		(b) *vs* (c)	
							U	*P*	*U*	*P*
LH (U/l)	12·0	(4·1– 26·0)	11·9	(3·1– 20·7)	5·7	(2·0– 10·2)	261	NS	74	<0·001
FSH (U/l)	4·7	(1·9– 8·0)	4·4	(1·4– 8·4)	5·8	(1·4– 18·4)	215	NS	208	NS
LH.FSH ratio	2·9	(1·0– 4·9)	2·5	(1·0– 5·8)	0·9	(0·5– 6·1)	227	NS	60	<0·001
Testosterone (nmol/l)	4·8	(1·5– 8·4)	2·9	(1·6– 5·5)	1·7	(0·8– 2·4)	121	0·004	45	<0·001
SHBG (nmol/l)	23·0	(11·0– 53·0)	35·0	(10·0– 90·0)	67·0	(32·0–111·0)	148	0·025	99	<0·001
FAI	19·4	(5·4– 35·5)	8·0	(3·6– 42·3)	2·8	(1·3– 5·0)	102	0·001	8	<0·001
Androstenedione (nmol/l)	14·0	(6·7– 21·0)	9·9	(5·7– 17·0)	8·0	(4·9– 10·0)	143	0·018	120	0·002
DHEAS (nmol/l)	6·2	(2·6– 20·9)	7·1	(2·8– 15·5)	4·5	(2·5– 10·3)	237	NS	140	0·008
E_2 (pmol/l)	178	(111 –278)	180	(101 – 717)	125	(60 –359)	227	NS	161	0·027
E_1 (pmol/l)	287	(156 –683)	265	(166 –1160)	196	(149 –441)	263	NS	110	<0·001

* Mann–Whitney *U*-test

Results are medians (range) values. SHBG = sex hormone binding globulin; FAI = free androgen index; DHEAS = dehydroepiandrosterone, E_2 = 17β-oestradiol, E_1 = oestrone NS = not significantly different

ferent classes of functional oligo-amenorrhoea (Fox *et al.* 1990).

Serum oestrogens in women with PCO are primarily ovarian in origin. Although the individual follicles in the polycystic ovary are hypoestrogenic (Erickson *et al.* 1979), studies of hormonal gradients across the ovary using selective catheterization of the ovarian vein indicate that in combination the numerous follicles generate substantial quantities of both E_2 and E_1 (Wajchenberg *et al.* 1988).

Although the differences between oestradiol concentrations in the women with and without PCO were statistically significant, the ranges overlapped too much for measurement of E_2 to be of value. This disparity between the ability of biochemical and biological tests of oestrogen state to differentiate PCO from non-PCO may reflect a difference in the free (unbound) fraction of E_2, which is higher in PCO because of reduced SHBG concentrations (Lobo *et al.* 1981), and the influence of other oestrogens particularly E_1 which is present in increased concentrations in PCO (Baird *et al.* 1977). Biological tests of oestrogen state appear to integrate the different components of the circulating oestrogen pool and the widely fluctuating levels within the individual, thereby providing an easily categorized index of oestrogenization as shown by Shulman *et al.* (1989) when they compared the outcome of progestogen challenge testing with ultrasound measurement of endometrial width.

The exceptional cases of PCO with clinical oestrogen deficiency raise several important points. Those with hirsutism appeared to have a more severe form of PCO as indicated by particularly high androgen levels, together with evidence of adrenal hypersecretion. In contrast, the two women with PCO and oestrogen deficiency but without hirsutism had a clear history of weight loss and stress as the precipitating cause of amenorrhoea. Hypothalamic dysfunction appeared to be overriding any disorder due to pre-existing PCO. We, and others (Conway *et al.* 1989), have also found PCO at scan in patients with hyperprolactinaemic amenorrhoea due to a pituitary adenoma. The incidental finding of PCO in such women is to be expected sometimes as it occurs in perhaps 20% of apparently normal women (Polson *et al.* 1988), who can otherwise only be identified clinically by careful definition of minimally increased cycle variation. Pharmacological suppression of pituitary function in women with PCO leads to a marked reduction in ovarian activity but no change in the essential structure of the ovary (Williams *et al.* 1989). The finding of PCO at scan in women with oligo-amenorrhoea can be misleading, therefore, and may lead to serious conditions such as anorexia nervosa and androgen-secreting tumours (Givens *et al.* 1975) being overlooked. When investigating women with oligo-amenorrhoea, it is more important to define endocrine function than ovarian morphology, though ideally a combined approach should be adopted.

Our results emphasize that many women with PCO presenting with oligo-amenorrhoea are not hirsute. Nevertheless, testosterone and androstenedione levels in the non-hirsute women with PCO were still markedly raised. Traditional teaching states that expression of hyperandrogenaemia as virilization depends upon peripheral conversion to dihydrotestosterone in androgen-dependent end-organs (Lobo *et al.* 1983). Although there was considerable overlap between the ranges of testosterone and androstenedione for the hirsute and non-hirsute patients with PCO, confirming that virilization is not simply related to the degree of hyperandrogenaemia, our data show distinct differences in androgen concentrations between the hirsute and non-hirsute sub-groups. The higher androgen levels in the hirsute group do not seem to be the result of any difference in LH levels, but might be related to obesity (Conway *et al.* 1989). It may be that higher insulin concentrations in obese patients with PCO (Fox 1990) sensitize ovarian thecal tissues to the androgenic action of LH (Barbieri *et al.* 1984).

With the advent of ultrasonography the true prevalence of PCO has been recognized and non-hirsute oestrogenized patients, often described as having 'defects of cycle initiation' or 'euestrogenic functional oligo-amenorrhoea,' can now be properly categorized. A greatly simplified classification emerges for the vast majority of anovulatory conditions from an ovarian standpoint.

Primary ovarian failure. This is characterized by raised FSH levels and oestrogen deficiency and is the result of several distinct causes ranging from dysgenesis to premature menopause and including surgery, irradiation and autoimmune disease. The clinical implications are all virtually the same.

Secondary ovarian failure. This results from hypothalamic or pituitary failure or disorders, including hyperprolactinaemia, and is typified by non-elevated FSH and LH levels and oestrogen deficiency. At ultrasonography the ovaries appear totally inactive or they have a multifollicular appearance (Adams *et al.* 1985). Occasionally, however, the acquired abnormality will be overriding pre-existing PCO.

Polycystic ovarian disease. This is increasingly recognized to be an inherited condition (Hague *et al.* 1988) that arises independently of any hypothalamic or pituitary disorder. It may occur as a primary ovarian condition (Polson *et al.* 1988) but is perhaps more often a manifestation of insulin resistance (Chang *et al.* 1983). The typical endocrine features are non-elevated FSH, oestrogenization (of the endometrium) and, less commonly, hirsutism.

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Polycystic ovaries: do these represent a specific endocrinopathy?

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Summary. Serum pituitary gonadotrophins, oestradiol, testosterone and insulin pulse patterns were examined at 15-min intervals for 6 h in 40 women with a previous diagnosis of polycystic ovarian disease (PCO) based on clinical, endocrinological and ultrasound data. Age, duration of symptoms, body mass index (BMI) and ovarian volume showed no correlation with the 6-h mean value of any hormone and testosterone blood levels did not correlate with those of insulin. Some patients had high and others low LH pulse pattern components, and few had an inverted LH:FSH ratio. Morphological polycystic ovarian changes may be a reflection of various rather than a single pattern of gonadotrophin secretion.

The aetiology and pathophysiology of polycystic ovarian disease (PCO) are poorly understood despite it being the most commonly diagnosed female endocrinopathy (Vaitukaitis 1983). The diagnosis may be imprecise since symptomatology is similar in such conditions as nutritional obesity, ovarian tumours and adrenal partial enzymatic deficiencies. Ultrasonically diagnosed polycystic ovarian changes are not specific and cannot be the sole criterion for diagnosis (Yen 1980; Swanson *et al.* 1981; Hann *et al.* 1984; Orsini *et al.* 1985). Random blood sampling in patients with PCO has demonstrated serum LH levels in the normal or even low-normal range (Gambell *et al.* 1973 and Duignan *et al.* 1975). Recently Conway *et al.* (1989) showed normal LH and testosterone values in 50% and 78% respectively of 556 women with ultrasonically diagnosed PCO However, the reliability of a single LH estimation is undermined by a variability of 38% and 92% in accuracy to represent the 6 h-mean value following 20 min blood sampling during the follicular and the luteal phases respectively in normal women (Santen & Bardin 1973). These authors suggested a minimum of 3-h multiple sampling to detect changes of 40% or less in LH concentrations. They also showed that 6-h mean values correlated perfectly ($r=1{\cdot}00$) with the integral levels determined by calculating the area under the curves. The mean coefficient of variation was 19±3·5% and 46±8·8% during the follicular and the luteal phases respectively. Studying six male subjects,

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Kulin *et al.* (1975) found that the coefficient of variation was 20% (range: 12–35%) for LH and 24% (range: 14–33%) for FSH. They also showed that a 3-h urine collection could be used as a simple, sensitive and accurate means of assessing circulating FSH and LH. High LH pulse amplitude with, or without, increased pulse frequency are new diagnostic criteria for PCO (Yen 1986; Waldstreicher *et al.* 1988). However, these were neither correlated with the body mass index (BMI), ovarian volume, pattern of microcysts distribution within the ovaries (echogenicity) nor to other biophysical data at presentation. It is evident that the criteria used for diagnosing PCO are not specific when assessed individually. Our objectives in this study were to examine the types of LH pulse pattern encountered in patients with PCO and to see if there was a universal pattern common to all of them. In addition, we attempted to relate hormone pulse pattern characteristics to patients' biophysical data (age, type and duration of menstrual dysfunction, presence or absence of hirsutism, ovarian volume and echogenicity). We also investigated the relation between the level of testosterone and insulin to test the thesis that impaired carbohydrate tolerance is androgen dependent in patients with PCO (Burghen *et al.* 1980).

Subjects and methods

Forty women aged between 19 and 35, with oligomenorrhoea or amenorrhoea attributable to PCO, consented to participate in the study. A diagnosis of PCO was made if there was hirsutism and/or serum testosterone ≥3·0 nmol/l, with serum LH level exceeding 10 IU/l and/or an LH/FSH ratio ≥2:1 (Yen 1980), and, in all cases, ultrasonic diagnosis of PCO (Adams 1986). Oligomenorrhoea was diagnosed if menstruation occurred every 6 weeks to 6 months whereas amenorrhoea indicated absent menstruation for more than 6 months. Hirsutism was scored according to the system described by Ferriman & Gallwey (1961). Scores exceeding 6, 10 and 14 indicated mild, moderate and severe hirsutism respectively. An Aloka Echo Camera LS-Model SSD-248 ultrasonic machine with 3·5 MHz sector probe was used to measure three ovarian diameters using the full urinary bladder technique. Ovarian volume was calculated as described by Campbell *et al.* (1982). It was suggested previously that the pattern of microcysts distribution within the ovaries might reflect the biochemical or clinical attributes of the syndrome (Yen 1986). In this study, we tested this hypothesis and examined whether the subtunical or cortical distribution of the microcysts within the ovaries had any bearing on these criteria. After the patient had fasted overnight, blood sampling at 15-min intervals was started at 0700 hours and lasted for 6 h on the fifth day of the menstrual cycle. Amenorrhoeic women were sampled after initial ultrasonic scanning to exclude the presence of a dominant follicle or corpus luteum, and after recording an anovulatory serum progesterone level of <10 nmol/l, assayed one day before multiple blood sampling. Blood samples (7 ml) were collected in plain tubes and allowed to clot at room temperature. Serum was separated and kept at −20°C for estimations of FSH, LH, oestradiol (E_2), testosterone and insulin, using radioimmunoassay.

FSH and LH were assayed using Amerlex-M kits (Amersham International, Amersham, UK). Testosterone was determined using RIA from RSL (Carson, California, USA). For oestradiol, ^{125}I-oestradiol direct (non-extraction) kits were used (Steranti Research Ltd, St. Albans, Herts, England). Serum insulin was measured by Pharmacia Insulin RIA-100 kits (Pharmacia Diagnostics AB, Uppsala, Sweden). The intra-assay coefficients of variation for all hormones ranged between 4·8 and 9·5% The valus of FSH and LH are expressed in mIU/ml as equivalents of the Second International Reference Preparation (IRP) 78/549 and the first IRP (68/40) respectively. Insulin standard was calibrated against research standard A for insulin, human, for immunoassays, 66/304 from the WHO International Laboratory for Biological Standards. Values are expressed in μU/ml. E_2 is expressed in pmol/l and testosterone in nmol/l.

Hormone pulse patterns were studied using the method described by Veldhuis *et al.* (1985). A false positive error rate of 2% was used to minimize type 2 error, as advised by these authors. The amplitude was the actual increase from nadir to peak during an identified pulse. The 6-h mean value for each hormone, together with the number and the average amplitude of pulses during the study time (6 h), were calculated. Admittedly 15-min blood sampling for 6-h periods does not provide an absolute estimate of the pulse frequency. However, it permits direct comparison between the different subgroups studied. Pearson's correlation coefficient (*r*) was used to study the correlation between the biophysical data and endocrine criteria after initial log transformation to attain non-significant

Table 1. Six-hour mean values (SD) of hormones, ovarian volume and body mass index (BMI) in various subgroups of patients with PCO.

	n	FSH (IU/l)	LH (IU/l)	E_2 (pmol/l)	Testo-sterone (nmol/l)	Insulin (μU/l)	Ovarian volume (cm^3)	BMI (kg/m^2)
Total group	40	4·7 (1·5)	11·6 (8·1)	186·0 (79·4)	4·0 (1·4)	9·8 (6·8)	15·7 (4·7)	29·1 (4·4)
Oligomenorrhoea	25	4·5 (1·3)	10·3 (6·0)	186·9 (96·2)	3·9 (1·4)	9·0 (6·7)	16·4 (5·3)	29.0 (4·2)
Amenorrhoea	15	4·8 (1·7)	13·8 (10·6)	184·5 (41·2)	4·2 (1·5)	10·9 (7·1)	14·8 (3·5)	29.2 (4·8)
Non-hirsutes	13	5·1 (1·6)	13·0 (10·9)	204·6 (119·1)	4·1 (1·3)	7·1 (4·1)	17·0 (5·1)	27.9 (4·6)
Hirsutes	27	4·3 (1·4)	10·9 (6·4)	117·0 (51·5)	4·0 (1·5)	11·0 (7·6)	15·2 (4·5)	29.7 (4·2)
Subtunical PCO	14	4·5 (1·5)	12·5 (10·6)	204·2 (102·7)	4·6 (1·7)	7·9 (6·4)	16·2 (4·8)	30.2 (5·4)
Cortical PCO	26	4·7 (1·5)	11·1 (6·5)	178·4 (64·5)	3·7 (1·2)	10·7 (7·0)	15·6 (4·7)	28 6 (3·7)

values for skewness and kurtosis ($P>0·05$). The Mann-Whitney *U* test was used to examine the difference between the different groups. Analysis of variance after log transformation was used to test the difference between patients with different grades of hirstutism. The Statistical Package for Social Sciences computer programme (SPSS/PC, 1987) was used for data analysis.

Results

Tables 1 and 2 show the means (SD) of the hormone levels, ovarian volume and BMI of the total population and subgroups of women studied. There were no significant differences between patients with oligomenorrhoea or amenorrhoea, and those with subtunical or cortical ovarian microcystic distribution or hirsute and non-hirsute women. As expected, analysis of variance showed severely hirsute patients ($n=9$) to have significantly higher mean testosterone values (5·7 SD 1·5) than mildly (mean 3·4, SD 1·0, $n=12$) and moderately hirsute women (mean 3·6 SD 1·0, $n=6$), ($P<0·02$). Moreover,

Table 2. Mean (SD) of pulse frequency (F)/6 h and pulse amplitude (A) of hormones in various subgroups of patients with PCO.

		FSH (IU/l)		LH (IU/l)		E_2 (pmol/l)	
	n	F	A	F	A	F	A
Total group	40	2·2 (1·7)	1 6 (1·1)	4·1 (1·4)	5·7 (3·5)	3·6 (1·7)	56·0 (28·4)
Oligomenorrhoea	25	2 0 (1·7)	1·3 (0·7)	4·3 (1·5)	5·2 (3·3)	3·7 (1·7)	58·7 (33·9)
Amenorrhoea	15	2·3 (1·7)	2·2 (1·5)	3·7 (1·2)	6·5 (3·8)	3·3 (1·5)	55·2 (16·2)
Non-hirsutes	13	1·6 (1·4)	1·5 (1·0)	3·9 (1 6)	5·3 (2·8)	4·0 (1·5)	60·5 (32·4)
Hirsutes	27	2·4 (1·8)	1·7 (1·2)	4·1 (1·3)	5·8 (3·9)	3·4 (1·7)	55 3 (26·7)
Subtunical PCO	14	2·6 (2·1)	1·6 (0·7)	4·1 (1·4)	5·4 (3·2)	3·7 (1·4)	63·3 (26·6)
Cortical PCO	26	1·9 (1·4)	1·7 (1·3)	4·1 (1·4)	5·8 (3·7)	3·5 (1·8)	53·5 (29·2)

		Testosterone (nmol/l)		Insulin (μU/ml)	
	n	F	A	F	A
Total group	40	3·3 (2·0)	3·2 (2·8)	3·8 (1·7)	5·7 (4·4)
Oligomenorrhoea	25	3·6 (2·1)	3 1 (1·9)	3·8 (1·5)	5·3 (4·5)
Amenorrhoea	15	2·7 (1·9)	3·4 (4·1)	3·8 (2·0)	6·4 (4·2)
Non-hirsutes	13	2·5 (2·0)	3·5 (3·9)	3·6 (1·8)	5·1 (5·2)
Hirsutes	27	3·7 (2·0)	3·0 (2·3)	3·9 (1·7)	6·0 (4·0)
Subtunical PCO	14	3·8 (2·2)	3·4 (2·2)	3·9 (1·9)	4·9 (3·4)
Cortical PCO	26	3·1 (2·0)	3·1 (3·2)	3·8 (1·6)	6·2 (4·8)

Table 3. Pearson's correlation coefficient (r) of age, duration of symptoms, body mass index (BMI), ovarian volume and 6-h mean values of hormones (n=40)

	Age	Duration	BMI	Volume	FSH	LH	E_2	Testosterone	Insulin
Age	—	0·46*	0·10	0·13	−0·03	0·18	0·14	−0·10	0·00
Duration	0·46*	—	−0·21	0·07	−0·32	−0·38	−0·00	0·22	−0·08
BMI	0·10	−0·21	—	−0·05	0·12	0·14	−0·09	−0·19	0·25
Volume	0·13	0·07	−0·05	—	0·38	0·13	−0·21	0·01	0·19

* P=0·01.

there was no significant correlation between 6-h mean testosterone values (r=−0·04), pulse amplitude (r=0·24), and frequency (r=0·08) with the corresponding insulin values in the total group. At the same time, there was no significant correlation between age, duration of symptoms, BMI, ovarian volume and the endocrine levels tested (Table 3).

Furthermore, analysis of the pulse pattern showed significant positive correlation between the LH (r=0·85), FSH (r=0·68), testosterone (r=0·54) and insulin (r=0·87) six-hour mean values and their respective mean pulse amplitudes (P<0·01). Except for LH (r=0·53) (P=0·01), all other hormones showed no significant correlation between their six-h mean values and pulse frequency. To test the pulse variability for each hormone, we calculated the coefficient of variation (SD/mean %) during the 6-h period. The mean values (with the 95% confidence intervals) for the 40 women were 14·7% (12·4 to 16·9%) for FSH, 26·8% (22·9 to 30·7%) for LH, 15·4% (13·0 to 17·2%) for E_2, 31·9% (26·5 to 37·3%) for testosterone and 31·3% (27·7 to 34·8%) for insulin.

Discussion

In this study, patient selection was based on the accepted clinical, endocrinological and ultrasonic criteria for diagnosing PCO. It is important to stress the high variability observed for both LH and testosterone (26·8% and 31·9% respectively) after calculating the coefficient of variation within the 6-h period. This confirms previous reports regarding the unreliability of single hormone estimations in representing the endocrine milieu (Santen & Bardin 1973). Also, one should point to the unique correlation, which was not shown by other hormones, among this group of women, between the LH pulse frequency with the 6-h mean values. Our findings suggest that bigger ovaries were not produced in response to prolonged duration of symptoms, higher LH levels or to any specific gonadotrophins pulse pattern. These ovaries did not produce more testosterone than smaller ones in this series. This confirms a previous report that normal sized ovaries may have the same histological and biochemical abnormalities as do enlarged ones in patients with PCO (Givens *et al.* 1976). It follows that ovarian size does not indicate severity of the PCO condition and that more elaborate treatment regimens are not indicated on the sole criterion of enlarged ovaries. We have already shown that women with larger polycystic ovaries needed less gonadotrophins for successful induction of ovulation (Abdel Gadir *et al.* 1990*a*). We also demonstrated that the microcyst distribution pattern within the ovaries has no endocrine significance. This contradicts a previous suggestion by Yen (1986) that ovarian morphology may reflect the clinical and/or endocrinological characteristics in patients with PCO.

Contrary to previous claims (Shoupe *et al.* 1983) we showed that hirsute patients with PCO did not have significantly higher serum insulin values than non-hirsute women. Moreover, there was no significant correlation between the 6-h mean testosterone values, pulse amplitude and frequency with the corresponding insulin values. This brings into question the theory that carbohydrate intolerance in women with PCO is androgen dependent. This point is supported by a previous finding that reducing serum testosterone after ovarian electrocautery or pituitary desensitization with a luteinizing hormone releasing hormone analogue was not associated with a reduction in serum insulin level in PCO patients (Abdel Gadir *et al.* 1990*b*). The lack of any significant difference in the 6-h mean testosterone values between hirsute and non-hirsute women might be due to our criteria for patient selection. All women in this study were hirsute and/or biochemically hyperandrogenic (testosterone ≥3·0 nmol/l). LH pulse criteria were found to be quite variable despite the initial common and stringent criteria used for diagnosis. Some patients had high or low LH pulse pattern components (as reflected by the relatively high standard deviation in the total group) and a few women had inverted LH:FSH ratio, despite a high ratio before the study. This may reflect a non-persistent or variable endocrine milieu at different times in the same women, despite synchronized blood sampling relative to the menstrual cycle. It may, in addition, reflect the lack of a constant universal pattern common to all women with PCO. This may raise some doubt on the accuracy of LH pulse studues in diagnosing PCO.

It can be concluded that BMI, ovarian volume and echogenicity have no bearing on the pulsatile pattern of the hormones studied. Evidence against a direct correlation between testosterone and insulin levels in women with PCO is presented. Women with PCO selected on the most stringent criteria did not show a universal LH pulse pattern common to all of them. This study confirmed the current concept of the heterogeneity of PCO, which may be a consequence of different hormonal pulse patterns rather than being associated with one charactertistic disturbance.

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The miscarriage clinic: an audit of the first year

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Summary. We preview the results of the first year in a Miscarriage Clinic set up in 1989 in an effort to improve the support and counselling of women who have a miscarriage. Of 381 patients referred, 79% attended. The only statistically significant difference between the women who attended and those who did not attend was in the proportion of women who had planned their pregnancies (65% versus 33%, $P<0{\cdot}01$). Of the 300 patients who attended, 4% reported no grief reaction; 75% experienced a reaction which had resolved within one month and 21% experienced a reaction which had not resolved. No factor was identified which could predict the duration of the grief reaction. This audit demonstrates that there is a strong demand and need for this service for couples who experience a miscarriage.

An important recent advance in obstetric care has been the improved support and counselling of couples bereaved following a perinatal death (Forrest *et al.* 1982; Giles 1985). There is also evidence that the grief response to early pregnancy loss can be equally profound and potentially more difficult to alleviate (Graves 1987; Turner 1989). Although miscarriage is the most common complication of pregnancy (Smith 1988), obstetricians have paid little attention to the counselling of women who miscarry.

In an attempt to improve the care given to couples experiencing a miscarriage, a new approach was adopted formally in this hospital in 1989. A concerted effort was made to increase the inpatient counselling and the provision of information. Women were also offered a follow-up appointment for a clinic separate from the hospital's other clinics. This involved the collaboration of obstetricians, midwives, social workers and the chaplaincy services. The purpose of this paper is to review our experience of the Miscarriage Clinic after the first year.

Subjects and methods

All the women referred to the Miscarriage Clinic in 1989 were studied. Before discharge from hospital those who were not attending a gynaecologist privately were offered an appointment one month after the miscarriage. The timing of the clinic was coordinated with the family planning and social work services. It was staffed by senior rather than junior nonconsultant doctors. This was achieved by the redeployment of existing staff. The women's partners were encouraged to attend. At the clinic, the previous counselling was reinforced, the woman was examined and a cervical smear taken. No specific investigation was offered unless there had been recurrent mis-

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Table 1. Comparison between women who attended and those who did not attend the Miscarriage Clinic

	Attenders ($n = 300$)	Non-Attenders ($n = 81$)	
Nulliparous	98 (33%)	22 (27%)	NS
Previous pregnancy loss	84 (28%)	24 (30%)	NS
Married	277 (92%)	69 (85%)	NS
< 20 years of age	3 (1%)	5 (6%)	NS
Planned pregnancy	195 (65%)	27 (33%)	$P<0{\cdot}01$

carriage. A datasheet was completed by the attending doctor for subsequent audit.

Results

In the 381 women studied, 27% miscarried between 4 and 8 weeks amenorrhoea, 53% between 9 and 12 weeks amenorrhoea and 20% between 12 and 24 weeks amenorrhoea. An evacuation of the retained products of conception was required in 92%. Of the 381 women offered an appointment for the clinic, 300 (79%) attended. The only significant difference recorded between those who attended and those who did not attend (Table 1) was in the proportion of women who had planned pregnancies (65% *vs*. 33%, $P<0{\cdot}01$).

The characteristics of the women who did and those who did not have a persistent grief reaction one month after the miscarriage are shown in Table 2. Of the 300 women who attended for follow-up, 4% reported no grief reaction, 75% experienced a reaction which had resolved and 21% experienced a reaction which had not resolved. No factor was found in the study which could identify those at risk of having a persistent grief reaction one month after the miscarriage. Even in those women attending the Miscarriage Clinic who had not planned their pregnancies ($n = 105$), the grief reaction had not resolved in 17% at one month. Of the attenders, 13% of nulliparous and 35% of parous women had had a previous miscarriage; of the non-attenders, 13% of nulliparous and 36% of parous women had had a previous miscarriage.

Discussion

This audit of the first year of the Miscarriage Clinic demonstrates that there is a strong demand for this new service amongst women who have a miscarriage. One month after the miscarriage, women frequently reported both resolved and unresolved grief reactions. No factors were identified which could predict those women who were likely to develop a prolonged grief reaction and who might benefit from additional support.

The physical care of women who miscarry is usually delivered with skill and efficiency. The psychological response to a miscarriage varies considerably and may depend on the woman's reproductive and social circumstances (Graves 1987). There are indications that women who miscarry get insufficient support from healthcare professionals, including obstetricians (Giles 1985; Leroy 1988). Problems that arise after early pregnancy loss may go unrecognized, especially if there is no hospital follow-up programme.

After a miscarriage, hospitals usually review only those women with a history of recurrent miscarriage. This may occur at clinics attended by mothers with healthy babies, a practice some women who have miscarried find insensitive and distressing (Leroy 1988). As far as we know an outpatient clinic dedicated to miscarriage follow-up has been reported only in a research setting and the findings were similar to ours (Hamilton 1989). Of 57 women, 74% were reviewed as outpatients 4–6 weeks after the miscarriage (Hamilton 1989). Most of the women reported symptoms consistent with a grief reaction and all who attended found the counselling beneficial.

In an American study of women after miscarriage, all 22 showed intense emotional reactions characterized by the seven stages of grief (Leppert & Pahlka 1984). The counsellors perceived that the grief reaction was as severe as that after

Table 2. Characteristics of women who did and those who did not have a persistent grief reaction one month after the miscarriage

	None or resolved ($n = 237$)	Persistent ($n = 63$)
Nulliparous	82 (35%)	16 (25%)
Previous pregnancy loss	65 (27%)	19 (30%)
Married	223 (94%)	54 (86%)
< 20 years of age	2 (1%)	1 (2%)
Planned pregnancy	150 (63%)	45 (71%)

There were no significant differences between the two groups.

a perinatal death. Counselling has been shown to help after a bereavement (Parkes 1985) and to shorten the duration of mourning after a perinatal death (Forrest *et al.* 1982), but bereavement clinics have been established only for couples experiencing late pregnancy loss (Giles 1985).

Our study suggests that hospitals could improve the quality of service delivered to couples experiencing a miscarriage. Improving the psychological support and counselling may be beneficial not only after the miscarriage, but potentially may also improve the outcome of the next pregnancy (Stray-Pedersen & Stray-Pedersen 1984). Healthcare professionals and the general public need more information about the psychological impact of miscarriage and further clinical research is required to determine the best management.

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Effect of cervical traction with a tenaculum on the uterocervical angle

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Summary. The effect of cervical traction on the uterocervical angle was measured radiographically in 24 women undergoing diagnostic curettage. A radio-opaque guidewire was inserted through the cervical canal into the uterine cavity and a lateral pelvic X-ray taken before and after traction. The traction force was measured with a spring-balance attached to the tenaculum. Cervical traction in a caudal direction (force 2 N) reduced the median uterocervical angle, from 75° to 10° (P = 0·001). Moderate cervical traction straightens the uterus and the routine use of a tenaculum theoretically makes insertion of an intrauterine device safer and the passage of an embryo transfer catheter less traumatic.

A tenaculum is always applied to the cervix when rigid instruments are passed into the uterus. When flexible instruments are passed through the cervix of unanaesthetized women many clinicians omit the tenaculum. Family planning specialists in particular have polarized yet passionately held views on the necessity of using a tenaculum when inserting an intrauterine contraceptive device (IUCD). It is intuitively believed that a tenaculum on the anterior cervical lip stabilizes the uterus, reduces the cervico-uterine angle and brings the uterus into an axial position. Minimizing the degree of anteversion or retroversion and decreasing the uterocervical angle should theoretically decrease the frequency of subendometrial insertions (Elstein 1982, Discussion p. 18) and thus reduce removal problems and perforation rates (Elstein 1982). However, tenaculum application is painful and heightens the women's perception to pain as an IUCD is inserted so that, theoretically, it could increase the occurrence and the severity of vasovagal shock. Consequently many practitioners use a tenaculum only in a minority of women (Elstein, 1982, Discussion p. 19).

Many in vitro fertilization (IVF) units do not use a tenaculum routinely when transferring embryos. The clinician is conscious of the emotional and physical trauma an IVF cycle inflicts and often attempts to minimize the discomfort of the final stage by passing the embryo transfer catheter without supporting the cervix. However, if the uterus is not straight, the catheter will be directed towards the anterior or posterior uterine wall, possibly damaging the endometrial lining. If traction was used routinely to straighten the uterus the implantation rate might improve.

A tenaculum undoubtedly stabilizes the cervix but there is very little objective information regarding the effect of cervical traction on the position of the uterus and cervix. When the pelvis is looked at through the laparoscope the fundus of the uterus appears to drop down towards the perineum when traction is applied to the cervix. The uterus either rotates around an axis defined by the pelvic floor or it simply straightens out. To determine which mechanism is involved we measured the utero-cervical angle before and after traction.

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We first measured the average traction used during an IUCD insertion, secondly, we ensured that our measuring technique did not affect uterine configuration and finally we measured the in vivo uterocervical angle before and during traction.

Subjects and methods

Measuring cervical traction during IUCD insertion

The vaginal axis traction normally applied when inserting an IUCD was measured in 10 women by interposing a spring gauge between the handle of a tenaculum and the operator's hand.

The effect of a guidewire on uterine shape

The effect of the guidewire on the uterine cervical angle was measured on hysterectomy specimens. The cervix was held in the horizontal plane so that the uterine fundus flopped forwards and a multipurpose, polythene, radio-opaque angiograph catheter (French 5·0 gauge J3/SFC-35-145 guidewire from a Digiflex angiograph set) was passed into the uterine cavity. Lateral radiographs were taken. Conray was injected through the catheter as it was withdrawn and a further radiograph was taken.

Effect of traction on the position and shape of the uterus

The effect of cervical traction was measured in 24 non-obese consenting patients undergoing elective diagnostic curettage. Under general anaesthesia the cervix was exposed, cleansed and a French 5 gauge J3/SFC-35-145 guidewire from a Digiflex angiograph set inserted into the uterine cavity. A Michelle clip temporarily marked the external cervical os. The speculum was removed and a lateral radiograph taken. A tenaculum was then applied to the anterior lip of the cervix and a further radiograph taken as caudal traction was applied. The traction was measured using a spring balance and was not allowed to exceed 2 N (the force normally applied when inserting an IUCD).

The total gonadal radiation exposure was approximately 2·4mSv (24R). From the radiographs the guidewires were traced onto transparencies. The position of the fundus with respect to the sacral promontory and the cervicovaginal and cervicouterine angle were measured. In this paper 0° represents a straight uterus and 180° represents a uterus that is fully flexed.

Ten films were impossible to interpret because of under-exposure. The remaining data were analysed statistically using the Wilcoxon matched-pair test. The study protocol was approved by the local ethics committee.

Results

Cervical traction during IUCD insertion

The mean traction applied during the insertion of an IUCD in our family planning clinic was found to be 2 N (SD 0·6).

The effect of a guidewire on uterine shape

The guidewire did not distort the cavity or affect the uterocervical angle of hysterectomy specimens. The uterocervical angle was unaltered by the guidewire in all five hysterectomy specimens (range ± 10°).

Effect of traction on position and shape of the uterus

Traction straightened the uterus. In all but one woman the utero-cervical angle decreased with traction (Fig. 1). The median uterocervical angle was 75°. Traction straightened the uterus and reduced the median angle to 10° ($P = 0{\cdot}001$). Even when the uterus was clinically axial and neither anteflexed or retroflexed, in one woman radiology demonstrated a uterocervical angle of 30° which reduced to 0° with traction (Fig. 2). As illustrated in Fig. 3 the uterine fundus moves away from the sacral promentory and the axis of the cervix comes into line with that of the vagina.

Discussion

It is intuitively believed that traction straightens the uterus but this has never been confirmed with direct measurements. The theoretical value of routine tenaculum use when inserting an IUCD has never been examined scientifically. This is because it would require a controlled clinical trial looking for rare endpoints such as perforation and this would involve a sample size in excess of 50 000. Consequently the effect of tenaculum usage will probably never be known. Nevertheless, in spite of the lack of clinical trials

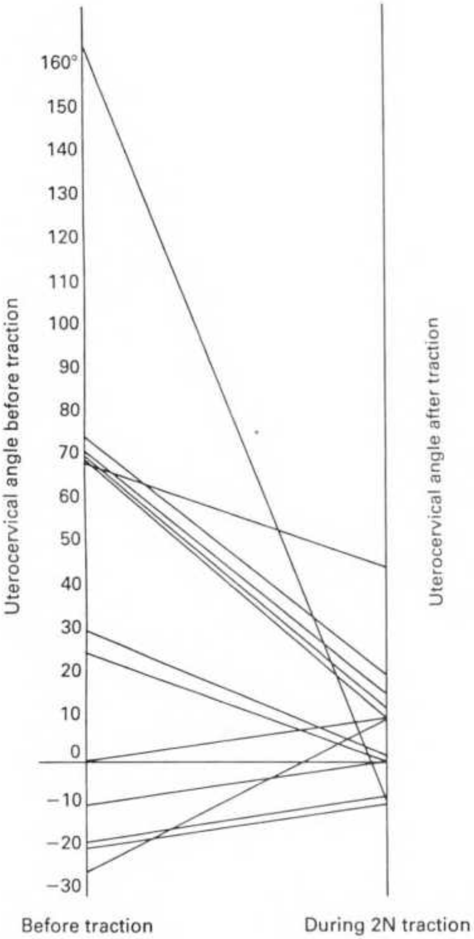

Fig. 1. The effect of a force of 2 N cervical traction on the uterocervical angle. An angle of 0° represents a straight uterus and an angle of 180° represents a uterus flexed so that the fundus touches the cervix. Angles from 0° to 160° describe an anteverted uterus and angles from 0° to −30° a retroverted uterus.

eminent specialists state that the omission of a tenaculum is 'astonishing' (Elstein 1982, Discussion p. 18), would render the doctor 'liable in the event of the occurrence of a mishap' (Elstein 1982) and 'that in every IUCD insertion, the uterus must be stabilized: we are doing our trainees a disservice if we train them any other way' (Elstein 1982, Discussion p. 19).

There is no argument that when the cervical axis is significantly out of line with that of the vagina a tenaculum can make any transcervical insertion technically easier. However, it is the angle between the body of the uterus and the cervix, not the vagina and cervix, that determines potential perforations and complications (Zakin *et al.* 1981). Cervical traction straightens the uterus and reduces the degree of retroversion or anteversion and this should reduce the number of difficult IUCD insertions (Snowden 1986).

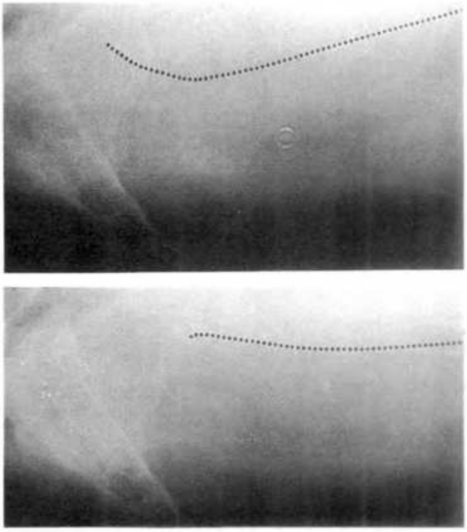

Fig. 2. Lateral pelvic radiograph before (above) and during (below) caudal cervical traction in a uterus that is clinically axial (guidewire is marked with dots).

Even when a clinical examination gave the

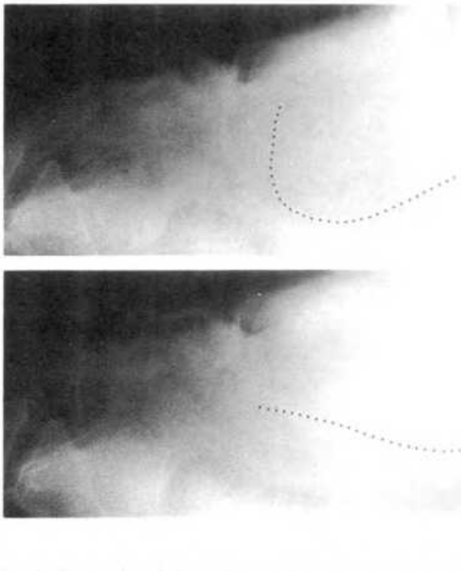

Fig. 3. Lateral pelvic radiograph before and during cervical traction in a flexed uterus.

erroneous impression that the uterus was straight, cervical traction reduced the degree of anteversion and retroversion and brought the uterus into line with that of the vagina. Consequently, when a tenaculum is not applied, any device that has to be passed into the uterus may have to negotiate an angle that may not be clinically apparent. An IUCD being inserted into a retroverted uterus could pass through the uterine wall, particularly if the trainee is already under the impression from the sound that the uterine fundus is 8 cm away.

Similarly, embryo transfer should be performed with cervical support using a tenaculum or another less traumatic instrument. If the uterocervical angle is not reduced to a minimum it is conceivable that insertion of an embryo transfer catheter could traumatize the delicate endometrium, become contaminated with blood and tissue and, theoretically, this could reduced conception rates.

For these two procedures we now need to train postgraduate staff to perform a bi-manual examination and stabilize the cervix with a tenaculum or an alternative instrument. Controlled clinical trials comparing two groups with and without tenaculum would consolidate our hypothesis, but our simple clinical observation suggests it is logical to use routinely an instrument to stabilize the cervix in every case rather than only on occasions as recommended by Loudon (Elstein 1982, Discussion p. 19).

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The use of cervicography in a primary screening service

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Summary. The cervicography and concurrent endocervical brush smear results obtained in 1162 women screened at the Marie Stopes Clinic were analysed. Colposcopy and biopsy results were obtained for positive cases. A comparison was made with a group of 1007 women attending the same clinic for routine cytology only. Nearly 10% of women who were screened by cervicography had a technically defective cervicogram, the main single reason being that the view was obscured by blood. Routine cytology was positive in 1%, while cervicography was positive in 13%, where positivity was defined as a result leading to a recommendation for colposcopy. The false positive rate for cervicography was 26%. Even after adjustment, this difference was highly significant ($P<0.0001$).

During the last 20 years, the lack of sensitivity and difficulties in quality control of cervical cytology have been highlighted in many studies (Husain *et al.* 1974; Morell *et al.* 1982). Overall false negative rates of 30% have been reported, while up to 58% has been quoted for women with grades 1 and 2 cervical intraepithelial neoplasia (CIN) (Giles *et al.* 1988). This has led to concern about its adequacy as a screening tool, and even to the suggestion that colposcopy might be used in screening, an idea which is impractical due to the shortage of colposcopists and the cost of the procedure.

Cervicography is a relatively new technique by which a photograph of the cervix, after the application of 5% acetic acid, is obtained without the aid of a colposcope (Stafl 1981). Since neither an expensive colposcope nor a highly trained colposcopist are required, the technique lends itself to use by any practitioner, medical or nursing, who is able to insert a speculum and inspect the cervix. The photographs obtained (cervicograms) are projected on a screen, thus obtaining a magnification and resolution comparable to that at colposcopy, and are interpreted by a colposcopist in much less time than it would take to perform a colposcopic examination.

It has been suggested that cervicography is suitable for use as a screening procedure and, indeed, has been used for this purpose for several years in the United States. Studies have shown it to be considerably more sensitive than cytology (Tawa *et al.* 1988). However, its major problem is a high false positive rate (81% in Tawa's study) when a reporting system of 'any abnormality' results in referral for colposcopy. For this reason, Adolf Stafl, in conjunction with the marketing company, National Testing Laboratories (NTL) has introduced a more structured report form, shown in Figure 1.

The Marie Stopes organization is a private

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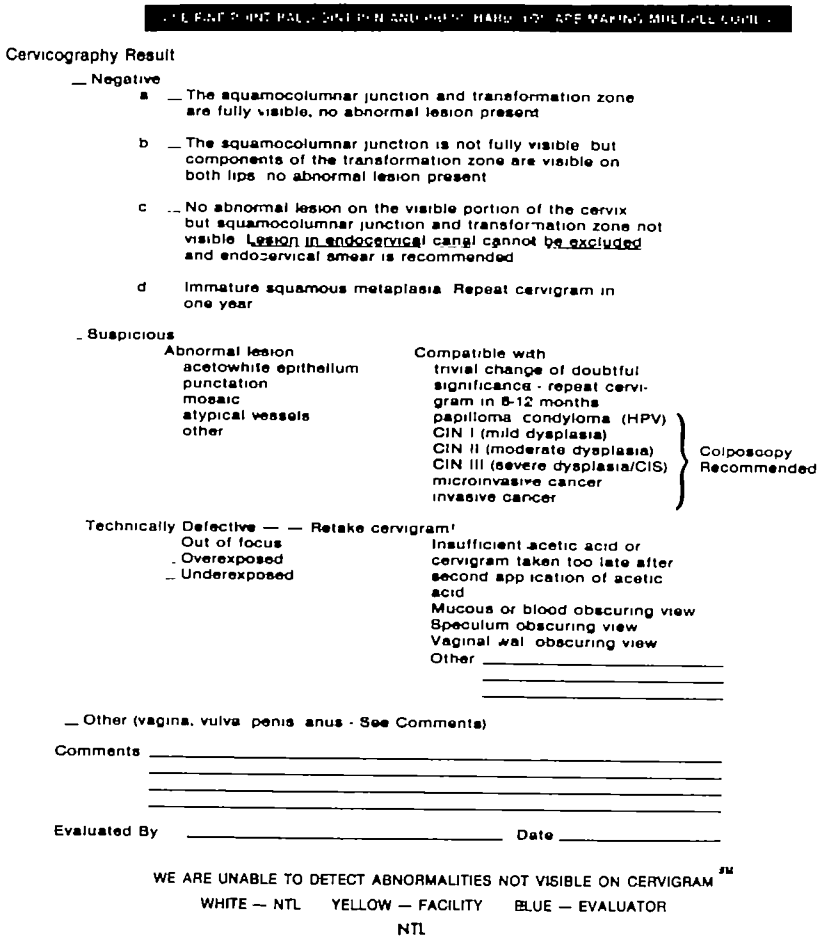

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Cervicography Result

_ Negative

a _ The squamocolumnar junction and transformation zone are fully visible, no abnormal lesion present

b _ The squamocolumnar junction is not fully visible but components of the transformation zone are visible on both lips no abnormal lesion present

c _ No abnormal lesion on the visible portion of the cervix but squamocolumnar junction and transformation zone not visible Lesion in endocervical canal cannot be excluded and endocervical smear is recommended

d Immature squamous metaplasia Repeat cervigram in one year

_ Suspicious

Abnormal lesion
acetowhite epithelium
punctation
mosaic
atypical vessels
other

Compatible with
trivial change of doubtful significance - repeat cervigram in 8-12 months
papilloma condyloma (HPV)
CIN I (mild dysplasia)
CIN II (moderate dysplasia)
CIN III (severe dysplasia/CIS)
microinvasive cancer
invasive cancer
} Colposcopy Recommended

Technically Defective — — Retake cervigram'
Out of focus
_ Overexposed
_ Underexposed

Insufficient acetic acid or cervigram taken too late after second application of acetic acid
Mucous or blood obscuring view
Speculum obscuring view
Vaginal wall obscuring view
Other ____________

_ Other (vagina, vulva penis anus - See Comments)

Comments ____________

Evaluated By ____________ Date ____________

WE ARE UNABLE TO DETECT ABNORMALITIES NOT VISIBLE ON CERVIGRAM SM

WHITE — NTL YELLOW — FACILITY BLUE — EVALUATOR

NTL

Fig. 1. Modified, structured cervicography report form used in the study

charity, offering a variety of family planning and well-woman services. Women do not require a letter of referral, and are therefore self-selected. In March 1988, Marie Stopes became the first centre in this country to offer cervicography as a primary screening service. NTL recommend a concurrent cervical smear, but it was decided that this should be an endocervical brush smear only, since information about the ectocervix would be available from the cervicogram.

Subjects and methods

All women who came for cervicography during the period March 1988 and December 1989 were included in the study. An endocervical brush smear was taken before the application of acetic acid. Two photographs were taken for each patient: the first after the application of 5% acetic acid and the second after the application of Lugol's iodine. The cervicography films were processed by NTL and reported on by their approved screeners. The screeners were not aware of the result of the smear.

Those women who were referred for colposcopy were followed up and the result of any biopsy obtained. Histology results were correlated with the smear and cervicogram reports.

Women come to Marie Stopes from all over the country, and are referred for colposcopy both privately and through the NHS. It was therefore not possible to ensure that the colposcopies and biopsies would be performed and analysed by the same practitioners and laboratories. Therefore, the results reflect the outcome of routine practice, rather than any special measures associated with a research study.

In order to provide some comparison with routine cytology, the cervical smear results of 1007 women who attended just before March

1988 were collected. These smears were obtained using a combination of a Jordan spatula and a Cytobrush (both samples on the same slide), which is routine practice in the clinic. Once again, these women were self referred. All the smears were reported in one laboratory.

Statistical methods

The age distributions were compared by a Wilcoxon rank sum test. Percentages were compared using a test for differences in proportions for binomial data without continuity correction and significance levels were based on the χ^2 distribution with 1 df.

Results

A total of 1162 women had cervicography, the results of which are shown in Table 1. Colposcopy was recommended in 13% and 11% were recommended to have a repeat cervicogram within a year. In 10%, the cervicogram was considered technically defective.

Because of the large number of reporting categories for cervicograms, smears and biopsies, these were simplified for the purposes of further analysis. Both smears and cervicograms were considered positive if the result led to a recommendation for colposcopy. Thus, smears were considered positive if they showed any degree of dyskaryosis, while cervicograms were considered positive if they indicated human papillomavirus infection (HPV), any degree of CIN or cancer.

Table 1. Cervicography results in 1162 women

Result	*n*	(%)
Negative A class	463	(39·9)
Negative B class	162	(14·0)
Negative C class	143	(12·3)
Negative D class	48	(4·1)
Trivial change	83	(7·1)
HPV	31	(2·7)
CIN 1	86	(7·4)
CIN 2	20	(1·7)
CIN 3	9	(0·8)
Microinvasion	2	(0·2)
Invasion	2	(0·2)
Out of focus	12	(1·0)
Underexposed	3	(0·3)
Too little acetic acid	22	(1·9)
Mucus/blood obscures view	48	(4·1)
Speculum obscures view	3	(0·3)
Vaginal wall obscures view	22	(1·9)
Technically defective, other cause	3	(0·3)
Total	1162	(100·0)

Table 2 shows the outcome of the screening service. A total of 112 women had biopsies as a result of a positive cervicogram, the results of which are shown in Table 3. It can be seen that the overall false positive rate of biopsied women is 17%. However, there were also 13 women in whom a positive cervicogram was followed by a negative colposcopy and no biopsy was taken (Table 4). If these are also considered to be false positives, the false positive rate increases to 26%.

Only 16 of the concurrent endocervical brush smears were positive; in three of these women the biopsy was negative, giving a false positive rate after biopsy of 19%. In two of these three the cervicogram was also positive, showing HPV/CIN 1. There were two other women who had a positive smear and a negative cervicogram, both smears showed mild dyskaryosis and histology showed HPV/CIN 1. In one of these, the cervicogram report was in fact Negative C class (brush smear recommended).

Nearly one in ten women (10%) had a technically defective cervicogram, resulting in a second visit for a repeat. Analysis of these shows several interesting features. The median age of women having technically defective cervicograms was 40 years, compared with 36 years for those women having satisfactory cervicograms. This difference was statistically significant, $z = 4{\cdot}38$, $P<0{\cdot}0001$).

Overall 42% of the defective cervicograms were due to blood or mucus obscuring the view and in 85% of these, blood was the responsible factor. The vaginal wall obscured the view in 19% of the defective cervicograms and this was more common in older women (median age 43 compared with 36 for those with satisfactory cervicograms, $z = 4{\cdot}38$, $P<0{\cdot}0001$).

Only 1% of the 1007 routine smears was positive, compared with 13% of the cervicograms.

Table 2. Outcome of the screening service

Outcome	*n*	(%)
No colposcopy	1007	(86·7)
Colposcopy and biopsy	130	(11·2)
Colposcopy negative, no biopsy	19	(1 6)
Colposcopy advised, results not traced	6	(0·5)
Total	1162	(100·0)

Table 3. Results of biopsy following a positive cervicogram

Biopsy result	*n*	(%)
Negative	19	(17·0)
HPV/CIN 1	67	(59·8)
CIN 2 or worse	26	(23·2)
Total	112	(100·0)

Table 4. Positive cervicograms where colposcopy was negative and no biopsy was taken

Cervicogram result	*n*	(%)
HPV	2	(15·4)
CIN 1	8	(61·5)
CIN 2	3	(23·1)
Total	13	(100·0)

Even if the false positive cervicograms are excluded, leaving a positivity rate of 10%, this difference is highly significant (χ^2 = 81·5 1 df, P<0·0001).

On further inspection we found that the positivity rate for cervicography was significantly higher (21%) in the first 4 months after its introduction, compared with the remainder of the study period (10%). This is presumably a result of the publicity at its launch, which may have attracted women already worried about the possibility of an abnormality. However, even after removal of the false positives, the positivity rate stabilized at around 8% after the first 4 months, which is still much higher than in the cytology-only group (χ^2 = 54·7, 1 df, P<0·0001). This can be partly explained by a slightly older age distribution in the cytology group (medians 36 *vs* 33 years) and somewhat higher parity (parity ≥ 2, 32·3% *vs* 16·2%, though the median parity in both groups was 0), but even after adjustment a substantial and highly significant difference remained (using a generalized linear model with binomial errors, χ^2 = 88·0, 1 df, P<0·0001).

Discussion

This analysis has shown that the revised reporting criteria for cervicograms have led to a major improvement in the false positive rate. Our rate of 26% compares very favourably with the 81% false positive rate found by Tawa *et al.* (1988), using the previous reporting criteria. It is also reassuring to note that this improvement occurred under routine working conditions.

It is not possible from our results to comment directly about the sensitivity of the smear compared with the cervicogram, since a full smear was not taken concurrently. However, previous cervicography studies have shown false negative rates of 42% (Spitzer *et al.* 1987) and 83% (Tawa *et al.* 1988) for cervical cytology. In this country, Giles *et al.* (1988) found an overall 32% false negative rate for the smear compared with colposcopy, and this rose to 58% for CIN 1 and CIN 2 lesions.

These figures are supported by our comparison with a group of women who had routine cytology at the same clinic. Although there is a small difference in age and parity between the two groups, the difference in positivity rates between them (1·0% *vs* 7·8%) is so great that it is unlikely these factors have had an important influence. A more serious potential bias may be due to self-selection. We have attempted to control for women who may have been attracted by the initial publicity and who might not have been a comparable group. The clinic also advertises its cytology services on a regular basis, and has done so for many years; in addition, it is the clinic's policy to advise referral for colposcopy after one, even mildly, abnormal smear. This makes it less likely that women would attend for cervicography in order to confirm a previous abnormal smear report.

Overall, 35% of the technically defective cervicograms were due to blood obscuring the view. It is reasonable to assume that this occurred as a result of the preceding smear. The smear could be taken after the cervicogram, but it has been shown that smears taken after the application of acetic acid are more likely to be unsatisfactory (Griffiths *et al.* 1989). It can be seen from the analysis of smear *vs* cervicogram that only two women, who had mild disease, would have been missed if the smear had not been taken. It could therefore be argued that if the concurrent smear was omitted, the reduction in technically defective cervicograms and the reduced cost of the procedure would compensate for the very slight loss in what is already a very high sensitivity.

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Splenic rupture in utero following a road traffic accident. Case report

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Case report

The patient, a 27-year-old married nurse, gravida 3, para 1, arrived in the accident and emergency department in the 36th week of pregnancy, having been involved in a road traffic accident 30 min earlier. She was the driver of a car that had run into the back of another, at about 35 mph. She was not wearing a seat-belt and was flung forward onto the steering wheel, taking most of the impact on her abdomen. She was complaining of upper abdominal discomfort but was otherwise well. She had felt fetal movement since the accident. Maternal observations were satisfactory, blood pressure 145/85 mmHg and pulse rate 90 beats/min. The fetal heart rate was ausculated at 120 beats/min. The maternal abdomen was soft, and the uterus neither tender nor irritable. There was no evidence of any other maternal injury She was transferred to the labour ward for cardiotography (CTG) and further reassurance.

The initial CTG recording showed a reactive fetal heart with a baseline rate of 160 beats/min. The maternal pulse was 110 beats/min at the time. An ultrasound scan showed a single, living fetus, presenting by the vertex. There was no obvious retro-placental haematoma. Because the patient continued to have abdominal discomfort and had palpable uterine contractions, she was kept on the labour ward for further observation. A clotting screen was normal. Ninety minutes after admission, a deceleration in the fetal heart rate to 80 beats/min was heard and was observed on the CTG recording. A portable ultrasound confirmed fetal bradycardia. She was delivered by caesarean section of a baby girl in poor condition; there was no evidence of placental abruption or cord entanglement. There were no signs of maternal intra-abdominal trauma. The baby weighed 2900 g, was white, floppy, and had a heart rate of 80 beats/min. She was intubated immediately, and then given both dextrose and bicarbonate intravenously. The infant had an Apgar score of 7 at 3 min. Her capillary blood values were pH 6·88, BE − 19.

The baby was admitted in the special care unit where an umbilical arterial line was established, blood taken for haemoglobin estimation, and further steps taken to correct the acidosis. The haemoglobin was 9·9 g/dl and 50 ml of whole blood was given and dopamine infusion was started at 5 μg/kg/min to improve renal perfusion.

At 3 h of age, the baby's condition again deteriorated, and it was becoming evident that there was progressive internal haemorrhage. An ultrasound examination excluded intracranial haemorrhage but suggested intra-abdominal bleeding, as there was free fluid around the liver and spleen. Peritoneal lavage revealed frank blood. At laparotomy, a small tear was found in the spleen and a splenectomy was performed. The infant suffered a cardiac arrest during surgery, but was resuscitated.

She was re-admitted to the special care baby unit post-operatively, but despite active measures died 24 h later. At post-mortem the cause of death was found to be disseminated intra-vascular coagulation.

Discussion

Estimates of the frequency of pregnant women being involved in motor accidents are difficult to

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make, but a series from California (Auerbach 1979) suggests that 6·9% of all pregnancies are complicated by an episode of blunt abdominal trauma, commonly sustained in road traffic accidents. Whilst in most of these incidents the injury is minimal and fetal well-being is not compromised, in a significant minority both the mother and fetus are injured, often fatally.

The question as to whether seat-belt restraints offers maternal and fetal protection has been examined by several authors. Crosby & Costiloe (1971) reported a series of 208 accidents involving pregnant women, only 28 of whom were wearing seat-belts of the lap-restraint type. They found no statistically significant increase in fetal loss in the restrained group. However, among the unrestrained group, both maternal and fetal loss increased if the woman was thrown from the vehicle. Studies by Crosby *et al.* (1972) showed that if the woman wore a three point harness (over the shoulders) fetal survival was improved. Pepperell *et al.* (1977) made similar observations as to the effectiveness of seat-belts in protecting from injury and concluded that severe extra-genital injuries could be reduced with improved maternal outcome, but that seat-belts may increase the risk of placental abruption.

Placental abruption would appear to be the commonest cause of fetal death if the mother survives the accident. The human placenta contains no elastic tissue, unlike the uterus, which responds to changing acceleration—deceleration forces by changing shape. Thus, shearing of the placenta may occur, particularly after blunt abdominal trauma sustained in car accidents where intrauterine pressure may exceed 500 mmHg (Higgins & Garite 1984). Several studies have reported placental abruption after a car accident and, usually, signs are evident within 48 h (Higgins & Garite 1984). The incidence is approximately 3·6% (Golan *et al.* 1980) following a car accident. In our patient there was no sign of external abdominal trauma, but her complaint of left upper quadrant pain, followed by uterine contractions suggested the possibility of abruption. This was not confirmed during the ultrasound examination nor at delivery.

Fetuses have been reported to have sustained skull and long-bone fractures, intra-cranial haemorrhage and soft tissue injury following accidents (Elliot 1966; Connor & Curran 1976; Stuart *et al.* 1980). In our patient intra-cranial haemorrhage was considered in view of her poor condition and low haemoglobin but was not confirmed by ultrasound examination.

Splenic rupture in-utero is a very rare injury, with only one other case having been found in the literature (Rothenberger, *et al.* 1978), which also resulted in a neonatal death.

Assessment of the pregnant woman following a road traffic accident can be difficult in an accident & emergency department, particularly when she can maintain a normal blood pressure despite moderate blood loss and the pregnant uterus makes assessment of other abdominal organs difficult. All personnel involved in the care of such women must consider both the mother and the fetus, perhaps more so if maternal injuries are minimal and admission to hospital is not apparently indicated. A satisfactory fetal heart recording at presentation can be falsely reassuring, as in our patient, and others noted by Stuart *et al.* (1980) Continuous monitoring for several hours may be necessary to detect fetal distress particularly when the patient complains of abdominal discomfort or uterine contractions.

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Seat belt injury in pregnancy resulting in fetal death. A need for education? Case reports

MALCOLM GRIFFITHS, GEORGINA HILLMAN,
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Case reports

Patient no. 1

A 30-year-old married woman in her fifth pregnancy was involved—at 36 weeks gestation—in a road traffic accident as a front seat passenger. She had been wearing a conventional three-point fixing seat-belt. She was admitted to the accident and emergency department, where she was noted to have marked bruising over the anterior chest wall and abdomen. She had multiple rib fractures. A laceration of her leg required suturing. There was evidence of a cervical whiplash injury. She began to bleed vaginally and was transferred immediately to the nearby maternity hospital. On arrival no fetal heart was heard. Fetal death was confirmed by ultrasound scan.

Having excluded any coagulation defect labour was accelerated with intravenous oxytocin. Fetal cells were seen on Kleihauer test. Blood loss was corrected by transfusion. After a short labour she had a spontaneous vertex delivery of a fresh stillborn girl (birthweight 2·668 kg), without apparent abnormalities. The placenta was delivered in two halves, bisected, half spontaneously, half by controlled cord traction.

Postmortem examination of the stillbirth revealed evidence of acute asphyxia. There was also bruising over the posterior skull. A large retro-placental clot was noted. Ultrasound scan in pregnancy had shown an anterior placenta.

The woman's recovery was complicated by a chest infection and pneumothorax, both presumed to be secondary to the rib fractures. She has had two subsequent uneventful pregnancies.

Patient no. 2

A 30-year-old married woman in her second pregnancy was involved—at 31 weeks gestation—in a road traffic accident—also as a front seat passenger. She too had been wearing a conventional seat-belt. She was initially seen by her general practitioner, who could not detect a fetal heart beat on auscultation. She was therefore referred directly to the maternity unit. The only apparent external injuries were marked bruising across the chest and abdomen. No fetal heart beat could be heard by a hand held Doppler fetal heart detector. There was no clinical suggestion of placental abruption. An ultrasound scan confirmed the absence of fetal heart beat. A Kleihauer test showed evidence of a large feto-maternal haemorrhage. Clotting studies showed no abnormality.

Labour was induced with extra-amniotic prostaglandin E_2, via a Foley catheter placed transcervically. After a 12 h labour she had a spontaneous vaginal delivery of a male fetus showing early signs of maceration.

The puerperium was uncomplicated. Histological examination of the placenta showed an area of organized retro-placental thrombus, with areas of adjacent intra-placental haemorrhage.

Discussion

There has been only one previous case report, in the British literature, of fetal death due to seat-belt injury (Fakhoury & Gibson 1986). Those

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authors supported the earlier recommendation of McCallum (1982), who suggested that pregnant women should sit on the lap-strap and only be restrained by the shoulder-strap (a suggestion with which we strongly disagree). It has been pointed out that this suggestion is 'positively dangerous' (Herbert 1982).

Seat-belt injury may cause fetal death either by direct fetal trauma; by placental trauma; or by maternal trauma leading to shock and secondary fetal asphyxia (Sherer & Schenker 1989). Both of our patients had evidence of placental trauma, in the first there was also fetal injury. We are not aware of any other reports demonstrating such striking evidence of placental injury, as the bisection which occurred in our first patient. Stuart *et al.* (1980) described two patients with less major placental laceration—one related to a lap only belt, the other in an unrestrained passenger. Although a number of examples of uterine rupture in motor accidents have been reported (Schoenfeld *et al.* 1987; Matthews 1975), this condition has only been seen in women wearing ill-fitting lap only restraints.

In the United Kingdom, front-seat passengers and drivers are required to wear seat-belts. These are almost invariably of the three-point fixing type. There is no doubt that in both of the accidents reported here the use of seat-belts saved the women from even more severe injury or death. However, the pattern of maternal injuries, in both these instances, suggests that the belts were not correctly fitted. General practitioners, obstetricians and midwives should encourage the use of properly adjusted seat-belts by all pregnant women, 'with the lap-strap as low as possible below the bulge' (Herbert 1982). The shoulder-strap should be above the uterine fundus, ideally lying between the breasts (Attico *et al.* 1986). With such a positioning no uterine or fetal trauma should occur. No major maternal trauma should result.

Together with the Royal Society for the Prevention of Accidents (R. Cummins, personal communication) we would urge that advice regarding seat-belts in pregnancy be included in the advice given in antenatal clinics and classes Pregnant women travelling in motor cars should always use seat-belts, such seat-belts should be correctly fitted.

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Theca-lutein ovarian cysts associated with placental chorioangioma. Case report

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Case report

A 30-year-old woman was admitted to the obstetric unit in the 26th week of gestation with rapidly developing hydramnios. She was primigravid and her pregnancy had been uneventful. This was a normal conception and she had never used ovulation induction drugs. Ultrasound scan showed a single normal fetus with an excessive amount of amniotic fluid. The fetal dimensions corresponded to the gestational age and there were no signs of fetal cardiac failure. The placenta was anterior and contained a well-circumscribed placental tumour measuring 6 × 6 × 7 cm, consistent with chorioangioma.

Two weeks later, at 28 weeks gestation, spontaneous preterm rupture of membranes occurred followed by the onset of regular uterine contractions. The fetus presented as a breech and its weight was estimated as 1300 g. Delivery by caesarean section was decided. The lower segment was well formed and a live female infant weighing 1350 g with Apgar scores of 1 and 5 at 1 and 5 min was born. The placenta and membranes were delivered by controlled cord traction. Both ovaries were enlarged to 8 × 8 cm by multiple theca-lutein cysts. Laparotomy revealed no other abnormality.

The placenta weighed 550 g and the umbilical cord had three vessels. The placental tumour weighed 250 g and measured 9 × 7 × 5 cm. The tumour was attached to the placenta by a short pedicle containing two vessels. Histopathology showed a chorioangioma with extensive infarction, probably secondary to thrombus that was found in the feeding artery.

Postoperative recovery was uneventful and the woman left the hospital 8 days after delivery. An ultrasound scan 6 weeks later showed that the ovaries were normal in size. The initial concentration of human chorionic gonadotrophin (hCG) was 709 500 mIU/ml at 26 weeks gestation This is much higher than the values observed in normal pregnancy by Aspillaga *et al.* (1983) who report a mean normal value of 10 000 mIU/ml at this gestation. Six weeks after delivery the hCG level was <5 mIU/ml. The presence of hCG in the placental chorioangioma was confirmed by immunohistochemistry although a semi-quantitative comparison with normal placental tissue could not be made because of tissue necrosis in the tumour.

The baby was managed in the neonatal unit and suffered some of the complications of immaturity—moderate respiratory distress syndrome, clinical sepsis, neonatal jaundice requiring phototherapy and a patent ductus arteriosus that closed with indomethacin therapy. The baby went home well 59 days after birth.

Discussion

Chorioangioma is a common primary tumour of the placenta but most tumours are small and are only detected by careful sectioning of the placenta (Wentworth 1965). Large tumours can be diagnosed by ultrasound (O'Malley *et al.* 1981) and may result in maternal and fetal complications. Hydramnios is the most frequently described complication and is reported to occur in about a third of all cases (Fox 1966) but other complications include fetal microangiopathic haemolytic anaemia with hydrops (Jones *et al.* 1972), intrauterine growth retardation (Hurwitz *et al.* 1983), fetal high output cardiac failure

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(Benson & Joseph 1961) and feto-maternal transfusion (Stiller & Skafish 1986).

As far as we know this is the first report of theca-lutein cysts in association with placental chorioangioma. Theca-lutein cysts of the ovary are most commonly associated with hydatidiform mole and choriocarcinoma. Only 49 cases of theca-lutein cysts unassociated with trophoblastic disease have been reported in the English language literature (Wajda *et al.* 1989). Of these, 11 occurred with hydrops fetalis (8 immunological and 3 non-immunological), 8 with multiple pregnancies and 30 in otherwise normal singleton pregnancies. The cause of this condition is unknown, but is believed to be related to either elevated levels of hCG or abnormal ovarian response to normal levels.

Elevated levels of hCG in trophoblastic disease, hydrops fetalis and in multiple pregnancy can be understood in terms of increased production by an enlarged placenta. In our patient the placenta was large for gestation but the hCG level was disproportionately raised and we speculate that the chorioangioma is the source of hCG.

Theca-lutein ovarian cysts are most often bilateral and are found incidentally at the time of caesarean section. It is essential to recognize the benign nature of these cysts at operation since excision of these large ovarian tumours can lead to loss of reproductive potential for the woman. Sixteen of the 49 cases reviewed by Wajda *et al.* (1989) had unnecessary surgery that resulted in sterilization. The natural history of these tumours is postpartum regression.

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Anti-platelet antibodies: a prognostic marker in pregnancies associated with lupus nephritis. Case reports

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Case reports

Patient no. 1

A 31-year-old woman with epilepsy and lupus nephritis was seen at 13 weeks gestation. Her obstetric history included two neonatal deaths, two miscarriages and one live birth. She was normotensive with no proteinuria. Her systemic lupus erythematosus (SLE) was inactive (Table 1) and she was taking prednisolone 10 mg, azathioprine 100 mg and carbamazepine 300 mg daily. At 23 weeks she developed hypertension, proteinuria and thrombocytopenia with a platelet count of 59 000/μl. Coagulation was normal and a bone marrow examination showed abundant active megakaryocytes. Her serum showed a high titre of anti-platelet antibodies (Table 1). Despite increasing the prednisolone dosage to 60 mg daily her platelet count fell to 39 000/μl. She had a stillbirth at 25 weeks gestation.

Patient no 2

A 35-year-old woman with lupus nephritis was seen at 15 weeks gestation when she was normotensive. Her obstetric history included one live birth, a neonatal death and a miscarriage. Her SLE was quiescent treated by prednisolone 10 mg daily. At 19 weeks prednisolone was increased and azathioprine 100 mg started because of worsening proteinuria and hypoalbuminaemia. At 26 weeks she developed hypertension and thrombocytopenia with a platelet count of 88 000/μl. Bone marrow examination showed many active megakaryocytes, and serum anti-platelet antibodies were present in high titre (Table 1). At 28 weeks gestation the platelet count decreased further to 29 000/μl and a caesarean section was performed, following a platelet transfusion. Her baby died 4 days later. Post-partum her thrombocytopenia was treated with human immunoglobulin (6 gm daily intravenously for 5 days) and 1 week after the delivery the platelet count had risen to 115 000/μl.

Comment

Severe thrombocytopenia is an infrequent complication of pregnancy in patients with SLE (Varner *et al.* 1983; Lockshin *et al.* 1985a). The thrombocytopenia is probably immune mediated and Lockshin *et al.* (1985b) reported antiplatelet antibodies in one out of two patients studied.

We report two patients with lupus nephritis, both of whom developed severe thrombocytopenia and antiplatelet antibodies leading to fetal loss at a time when their lupus was serologically inactive. In both women the development of thrombocytopenia coincided with increasing hypertension and proteinuria suggesting a possible diagnosis of severe pre-eclampsia. However, they both had high titres of anti-platelet antibodies as well as a bone marrow with many active megakaryocytes indicating that their

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Table 1. Systemic lupus erythematosus activity in early pregnancy and at time of fetal loss

		Patient no. 1		Patient no. 2	
Variable	Normal range	Early pregnancy	Fetal loss	Early pregnancy	Fetal loss
C_3 (g/l)	0·75–1·75	0·93	0·97	0·99	0·74
C_4 (g/l)	0·14–0·54	0·23	0·24	0·27	0·22
ds DNA binding	<10%	Neg	Neg	15%	Neg
Antinuclear antibodies		Neg	Neg	Pos	Neg
Cardiolipin antibodies		IgG Pos IgM Neg	IgG Pos	ND	ND
24-h urinary protein		Not detected	5 g	Trace	15 g
Platelets ($\times 10^9$/l)		125	39	204	29
Platelet antibody		ND		ND	
IgM (fg/plt)	0–4·0		33·4		18 7
IgG (fg/plt)	0–8·5		14·31		19·24

ND = not done. plt = platelet. C_3 = Compliment 3. C_4 = Compliment 4.

thrombocytopenia was due to immune mediated platelet destruction.

Severe thrombocytopenia developed in both of our patients during treatment with prednisolone and azathioprine and this worsened despite an increased dose of steroids. In our second patient the platelet count rose in the postpartum period only after she was treated with intravenous immunoglobulin. Immunoglobulin given antenatally might have reversed the thrombocytopenia. In view of the high associated fetal mortality that we report, such therapy might be considered in future to correct thrombocytopenia and to allow greater fetal maturity before the delivery. Whether immunoglobulin given antenatally may have an adverse effect on the fetal immune system is not known.

Antibody mediated thrombocytopenia presents two potential problems in pregnancy. First these antibodies may pass to the fetus causing thrombocytopenia. Caesarean section has been advocated to avoid the increased risk of intracerebral haemorrhage due to thrombocytopenia at delivery, although its value has not been established (Horger & Moulton 1979). In our second patient the neonatal platelet count was normal, but neonatal thrombocytopenia occurs in as many as 67% of pregnancies with immunological thrombocytopenia. Treatment is necessary in only a minority of affected babies (Horger & Moulton 1979).

Second, maternal haemorrhage may complicate operative delivery. Platelet transfusion is only necessary before surgery, or to manage acute bleeding, as transfused platelets are rapidly destroyed by antibodies (Horger & Moulton 1979).

Several autoantibodies in SLE are of prognostic significance during pregnancy. Anti-Ro antibodies are strongly associated with congenital heart block (Gleicher 1986) and the lupus anticoagulant and anticardiolipin antibodies are associated with fetal loss (Gleicher 1986; and Lockshin *et al.* 1985b). Our findings suggest that antiplatelet antibodies are also associated with poor fetal outcome, and agree with the high fetal loss in previous reports (Lockshin *et al.* 1985a).

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SHORT COMMUNICATIONS

Tuboscopy in a previously sterilized patient

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Tuboscopy has been safely used to assess the tubal lumen of patients with a hydrosalpinx (Puttemans *et al.* 1987) and infertility (Brosens *et al.* 1987, De Bruyne *et al.* 1989). We present findings in a woman with a previous sterilization that suggest that tuboscopy may be of value in the assessment of women requesting reversal of sterilization, a procedure known to be associated with a significant risk of ectopic pregnancy (Winston 1981).

Case history

A woman aged 46 with three children was undergoing a total abdominal hysterectomy because of uterine fibroids. She had been sterilized and both fallopian tubes showed evidence of the previous modified Pomeroy tubal ligation but with no adhesions to neighbouring tissues. The proximal and distal ends of both fallopian tubes were of sufficient length for re-anastomosis.

Using a Stortz 26001 tuboscope, inserted through the fimbriated end, the right and left distal tubal lumens had different appearances. The right tube (Fig. 1) had normal folds right up to the site of the tubal ligation. Normal mucosal vascularity was present, and there were no apparent intratubal adhesions. In contrast, the left tube contained multiple intratubal adhesions with disruption of the mucosal folds (Fig. 2).

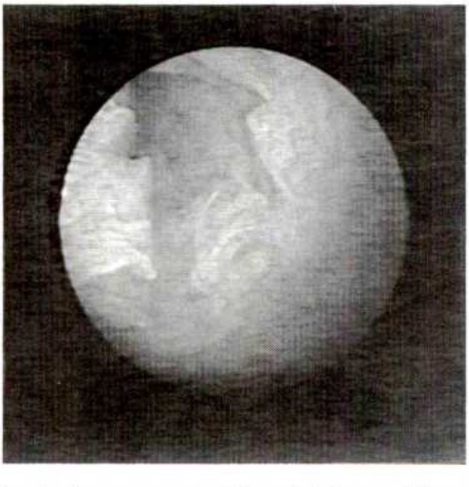

Fig. 1. Appearance of right tubal lumen. Normal appearance as far as the site of tubal occlusion (upper centre).

Comment

If this woman had requested reversal of sterilization, the laparoscopic appearances would have suggested this to be technically feasible. However, the tuboscopic appearances suggested that a simple tubal re-anastomosis on the left side would not have been successful and might have

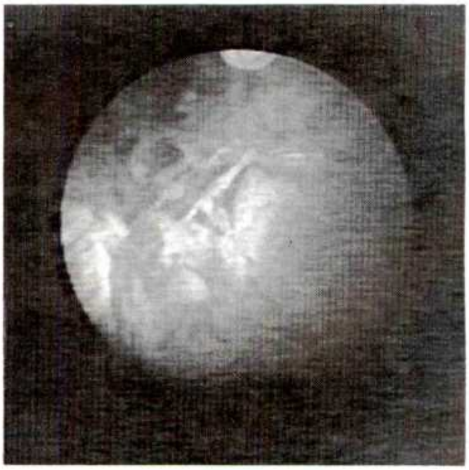

Fig. 2. Left tubal lumen showing thin bands of adhesions attached to the edge of major mucosal fold which runs across the upper aspect of the image from left to right.

Correspondence: S. D. Maguiness

resulted in an ectopic pregnancy. These findings suggest that inspection of the tubal mucosa by tuboscopy may form a valuable part of the assessment of women requesting reversal of sterilization.

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Role of menstrual blood loss measurements in management of complaints of excessive menstrual bleeding

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Overall 31% of women of reproductive age in the United Kingdom complain of excessive menstrual bleeding (MORI survey 1990). The complaint may lead to hospital referral and excessive bleeding is the main presenting symptom in one third of all referrals to gynaecology outpatients (Coulter *et al.* 1989). Clinical management is based on personal assessment by the patient of her menstrual blood loss rather than any objective measurement. But it is well established that women are poor judges of their menstrual loss: only 40% of women complaining of excessive bleeding have objective menorrhagia with blood losses greather than 80 ml in each menstruation (Fraser *et al.* 1984; Hallberg *et al.* 1966). Therefore in objective terms 60% of women complaining of excessive bleeding are receiving unnecessary treatment. Menstrual blood loss measurements are not routinely used in clinical practice and many gynaecologists dispute whether women complaining of excessive bleeding and found objectively to have a normal blood loss will accept this finding. It was therefore decided to undertake a pilot study to examine whether the finding of a normal menstrual blood loss in women complaining of excessive bleeding influenced clinical management.

Patients, methods and results

Seventeen patients, aged 30–45 years, were recruited from the John Radcliffe Hospital Gynaecology clinics, as part of study of menorrhagia, where the rate of objective menorrhagia (>80 ml blood loss per menstruation) was 54% of referrals. All had been referred complaining of regular heavy periods with no intermenstrual bleeding for assessment, with a view to hysterectomy. Pelvic examination was normal and none was using hormonal or intrauterine contraception, nor taking treatment for menstrual disorders at the time of assessment. Menstrual blood loss was measured using the alkaline haematin technique for two consecutive menstruations (Hallberg & Nilsson 1964). All the women had a normal blood loss (<80 ml) with a range of 15–60 ml (Hallberg *et al.* 1966). They were advised that their menstrual blood loss was within normal limits, did not constitute harm to their health and required no treatment. They were discharged from the hospital clinics and their general practitioners informed of their menstrual blood loss result.

Three years later they were contacted and it was found that 14 had accepted the advice and

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Correspondence: Margaret C. P. Rees

had received no treatment. Two were taking mefenamic acid, and one had undergone hysterectomy.

Discussion

Complaints of excessive menstrual bleeding lead to a large demand on health resources with regard to both drug and surgical treatment. In the year 1989–1990, about 672 000 prescriptions were made for excessive bleeding in the United Kingdom. Some 20 000 hysterectomies are performed per year for complaints of excessive bleeding in National Health Service hospitals in England and Wales. It can be argued that half of the treatments could be avoided by using objective menstrual blood loss measurements on which to base clinical management strategies.

This pilot study shows that women complaining of excessive menstrual bleeding can accept the finding that their menstrual blood loss is within normal limits and 16 of a potential 17 hysterectomies were avoided. Further study is required with larger numbers to assess the use of objective menstrual blood measurement in routine clinical practice.

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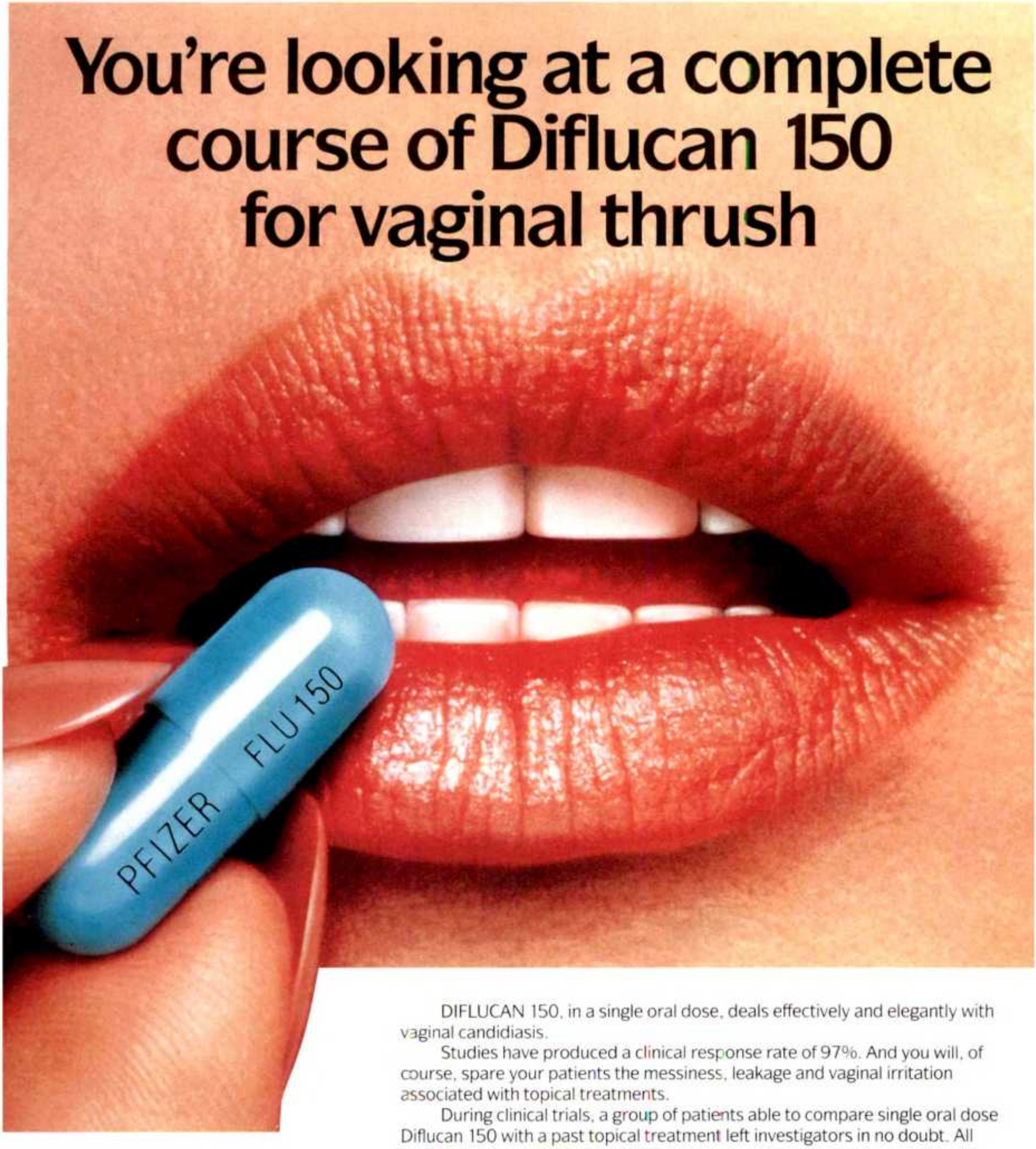

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ADONIS 030654569100082M

CORRESPONDENCE

Vitamin B6 in the treatment of the premenstrual syndrome—review

Dear Sir,
The review by Kleijnen *et al.* [*Br J Obstet Gynaecol* **97**, (1990) 847–852] was timely and useful but, unfortunately, incomplete.

Though their literature search revealed 12 double-blind placebo controlled trials on vitamin B6, I know of at least one further trial which showed no benefit over placebo (O'Brien 1987).

This was a double-blind cross-over trial comparing 100 mg of pyridoxine per day for two menstrual cycles with placebo. This was published in a book and therefore may have been missed during standard literature searches.

Furthermore, there have been three double-blind, placebo-controlled trials on a vitamin B6-rich multivitamin/multimineral supplement, Optivite. (Chakmakjian *et al.* 1985, Stewart 1987). This preparation, at an average dosage of six tablets per day throughout the menstrual cycle, which provides 300 mg of pyriodixine, together with other vitamins and minerals, especially magnesium, was found to have a beneficial effect compared with placebo over three menstrual cycles in two of the trials (Chakmakjian *et al.* 1985, Stewart 1987), but not when the dosage was reduced to three tablets a day (150 mg of pyridoxine, together with vitamins and minerals) for four menstrual cycles (Stewart 1987).

I would submit that a more formal and thorough analysis of the outcome of published trials of pyridoxine in the premenstrual syndrome (PMS) needs to be undertaken before its exact worth can be determined.

Furthermore, consideration should be given to the potential interaction between vitamin B6 and other nutrients, especially magnesium, as lowered levels in erythrocytes, but not serum, have been found in patients with PMS (Abraham & Lubran 1981, Sherwood *et al.* 1986, Stewart & Howard 1986). This may be particularly relevant as vitamin B6 deficiency, and for that matter, hormonal disturbances, are not found more frequently in women with PMS when compared with controls. The question of the value of nutritional supplements in PMS is I suggest still an unanswered one.

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Authors' reply

Dear Sir,
Dr Stewart mentions another controlled trial of vitamin B6 which we unfortunately missed in our search of the literature. It concerns a cross-over trial in 53 patients (O'Brien 1987). No significant differences between vitamin B6 and placebo were found on PMS symptoms. The description of the women's symptomatology, the methodology and the results are very limited and, consequently, the methodological score not very high.

We do not think that 'a more formal and thorough analysis' of the outcome(s) of published trials would yield new insights into the efficacy of vitamin B6 in PMS. In our opinion only the results of better designed new trials with parallel groups would be of value.

Three other studies have been reported involving a vitamin B6-rich multi-vitamin preparation (Stewart 1987, Chakmakjian *et al.* 1985). We did not include trials with such supplements, because our interest was in the effects of vitamin B6 alone. The supplement in question contains 31 different vitamins, minerals and other substances, mostly in megadosages. It would indeed be interesting to see whether combinations of, for instance, vitamin B6 and magnesium would show other effects than vitamin B6 alone.

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Correction

In our article, the second sentence of the discussion section should be read as follows: 'Furthermore, compliance, blinding and prognostic comparability was checked in only 3, 0 and 4 trials respectively.'

Methodological assessment is as follows:

Table 1. Methodological criteria

Study	A	B	C	D	E	F	G	H	I	J	TNI
Vitamin B6											
O'Brien (1987)	–	+	–	–	–	+	+	–	–	–	3
Multi-vitamin supplement											
Stewart (1987)*	±	+	–	+	–	±	±	+	±	–	5
Stewart (1987)†	±	+	–	+	–	+	+	+	±	–	6
Chakmakjian *et al.* (1985)	+	–	–	+	–	+	+	+	–	+	6

* = high dose trial; † = low dose trial, + = item is scored; – = item is not scored; ± = item is partly scored; TNI = total number of items which were scored.

A = patient characteristics adequately described (description of symptoms, duration, severity, and previous treatments); B = ≥50, women in each group; C = prestratification (matching) on relevant prognostic factors; D = randomization; E = check of prognostic comparability; F = subjects blinded, G = assessor blinded; H = effect measurement well described (reproducible); I = use of other concurrent treatments or vitamins has been checked; J = presentation of the results in such a manner that the analysis can be checked by the reader.

References for both letters

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ADONIS 030654569100083Z

Normal early pregnancy: serum hCG levels and vaginal ultrasonography findings

Dear Sir,

We would welcome the opportunity to comment on the interesting paper by Cacciatore *et al.* regarding the vaginal sonographic findings in early pregnancy following conception in natural cycles and cycles of ovulation induction [*Br J Obstet Gynaecol* (1990) **97,** 899–903]. The day of ovulation was defined as the day of the LH surge or hCG administration and the gestational age was estimated from this time with 14 days added. The authors stated that the gestation sac could be detected reliably by day 33, the yolk sac by day 38 and the fetal heart by day 43.

In our ongoing study of early pregnancy established after in vitro fertilization and embryo transfer we date the pregnancy from the day of oocyte retrieval (OR), 34 h after hCG administration. Gestational age is estimated by adding 14 days. Vaginal sonography is performed by experienced medical staff every 2 days using a Kretz Combison 310 with 5 and 7·5 MHz transducers. The gestation sac is seen reliably by day 36, the yolk sac by day 40 and the fetal heart by day 44.

It is hard to explain the evident discrepancy in the findings especially since if we were to define the day of ovulation in the same way as Cacciatore, the milestones would be reached 1 or 2 days later still in our study. We define the sonographic appearance of a gestation sac in the same way as Cacciatore and the sacs are the same size (1–3mm) when first seen. We are confident of our competence with vaginal sonography and have confidence in the machine that we use. We would, however, welcome further details of the Aloka and Hitachi scanners used by Cacciatore in case they have better definition at high magnification. Even if they did, we doubt this could account for the difference in results.

We feel it is most likely that the discrepancy is due to genuine differences in estimated gestational age resulting from the different mode of conception. We shall be able to comment on this further upon completion of our study. In the meantime clinicians should be wary of being too hasty in diagnosing a non viable pregnancy.

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Reference

Cacciatore B., Tiitinen A., Stenman U.-H & Ylostalo P. (1990) Normal early pregnancy: serum hCG levels and vaginal ultrasonography findings. *Br J Obstet Gynaecol* 97, 899-903.

Authors' reply

Dear Sir,
We thank Dr Perks and colleagues for their comments on our report. An important difference between our study and their study is that we investigated only women who conceived after normal intercourse. The interesting results of Perks *et al.* would indicate that a very early early gestational sac (1–3 mm) may become visible at vaginal ultrasonography 1–2 days later in IVF pregnancies than in those conceived normally. In IVF, the embryo is transferred about 2 days after oocyte pickup, 3–4 days after hCG administration, and embryos at different stage of development are often transferred. In addition it is possible that the blastocyst cavity expands more slowly becoming visible as a gestational sac slightly later than in pregnancies conceived naturally. Implantation might also occur slightly later in some IVF pregnancies. Reference to serum hCG levels would have been helpful but these data are not provided by Dr Perks.

Part of the difference could be due to technical differences in the equipment used. We used the Aloka SSD 630 and 650 and Hitachi 410 and 450 ultrasound equipment, which have electronically focused convex endovaginal transducers with an emission frequency of 5·0 MHz and 6·5 MHz respectively. Perks *et al.* had a transducer that used a higher frequency and which may have been capable of slightly better definition. We think this might account only for slight differences in results. In addition the size of the gestational sac detected was the same as in our study.

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Early identification of placenta praevia

Dear Sir

I read with interest the short communication by McClure & Dornan [*Br J Obstet Gynaecol* (1990) **97**, 959-961] on the poor predictive value of 18-weeks ultrasound scans for placenta praevia in the last trimester. I note from their paper that 18 weeks was the mean value, the range being 16 to 20 weeks. I performed a similar survey of low placentas on booking scans at Mill Road Maternity Hospital, Liverpool in 1989. For 777 scans recorded between 15 and 20 weeks the frequency of low placentation was 19%, with a marked fall with advancing gestation.

All scans were performed by trained radiographers and the assessment was subjective. The survey showed that the effect of delaying the booking scan from 16 to 18 weeks was a 50% reduction in the need for a repeat, probably unnecessary, scan at 32 weeks. It would seem that differential uterine growth may start earlier in pregnancy than has been suggested.

Table 1. Frequency of low placentation by gestation

Gestation (weeks)	No. of scans	Low placentation *n* (%)
15	110	26 (24)
16	382	82 (21)
17	184	35 (19)
18	51	6 (12)
19	38	2 (5)
20	12	0

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Reference

McClure N. & Dornan J. C. (1990) Early identification of placenta praevia. *Br J Obstet Gynaecol* **97**, 959–961

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Has in vitro fertilization made salpingoscopy obsolete? (Commentary)

Dear Sir,

I have read the correspondence [*Br J Obstet Gynaecol* (1990) **97**, 1064–1067] arising from the above Commentary and the paper by Watson *et al.* (1990) on which the Commentary was based. As one of the gynaecological surgeons whose results were included in the Watson *et al.* (1990) study and as the Director of the IVF programme subsequently referred to by Professor Lilford in the correspondence, I feel that I must have some say in this debate.

Only one of the correspondents (Mr H. E. Reiss) refers to the preferences of the patients in this matter. He believes that the majority of women with tubal occlusion would prefer the surgery and retain IVF as 'the last resort'. In my experience the choice made by the patient is very heavily coloured by the advice of the gynaecologist diagnosing the tubal occlusion. At the time when our IVF programme was purely a pilot scheme (including the last year only of the Watson *et al.* study), we received a large number of referrals from surrounding districts. The patients had often been told that there was no point in them undergoing tubal surgery because of its inherent low success rate and they would be much better off having IVF. These women were being consigned to an indefinite waiting list and, in effect, refused any form of treatment. I have no doubt that in the referring hospitals a considerable amount of money was saved by the non-performance of tubal surgery and yet the same referring districts have persistently declined to cross-fund for their patients to receive IVF in this unit.

At that stage of the development of our programme I felt very strongly that the diagnosis of tubal occlusive disease demanded two actions to be made. Firstly, arrangements for tubal surgery and, secondly and concurrently, inclusion in an IVF waiting list. Knowing the sort of duration of wait that these patients could expect, this allowed ample time for tubal surgery to be performed on the basis of clinical selection and the possible outcome of that surgery to be assessed. Even given very low success rates in the hands of the local gynaecologist this would have been preferable to an interminable wait for NHS IVF treatment. This is particularly so bearing in mind that during the waiting time the patient's age will be inexorably increasing and her likely chances of successful IVF treatment therefore decreasing.

One colleague in a neighbouring district has adopted this policy, others have not. Fortunately nothing remains static in medicine and the point raised by Burke & Nwosu (1990) in the correspondence regarding the statistics from our own IVF programme has been dealt with by Professor Lilford. In fact the more recent figures show a 38% pregnancy rate per embryo transfer in women aged 34 and under. Under these circumstances I would entirely support Professor Lilford's conclusion that in vitro fertilization is the treatment of choice for *most* forms of tubal occlusion. However, that does not mean that tubal surgery should be withheld from a patient for whom IVF with that sort of success rate is not available. There are a considerable number of people in the country at the moment who fall into that category because, not being able to afford private sector treatment, they happen to live in a Health District which refuses to purchase effective treatment for their particular disease state.

I would also like to support Mr Reiss' plea for more resourcing of programmes aimed at reducing tubal and other forms of infertility. Better education and wider screening for subclinical genital infection are both needed. Experimental work in these fields (Ashton 1989, Sprague *et al.* 1990) must be extended and it is hoped that the new Health Service structure will allow adequate funding for the prevention of infertility. Certainly I can see little evidence of adequate funding for its treatment.

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British Journal of Obstetrics and Gynaecology
March 1991, Vol. 98, pp 333–334

ADONIS 0306545691000866

Pain relief in labour. Commentary

Dear Sir,

Dr Reynolds gave a balanced comment on the need for analgesia in labour and the various modalities for its administration [*Br J Obstet Gynaecol* (1990) **97**, 757–759]. She did not consider the possible benefits derived from one-to-one nursing and of psychoprophylaxis (Freeman *et al.* 1986; Davidson 1962).

When these techniques are practised along with a guarantee that labour will not last longer than 12 h and active management of labour, in the National Maternity Hospital, Dublin, epidural rates of 12% in primigravidas and 3·4% in multigravidas are obtained (Stronge 1989). Such techniques may play a considerable role in reducing analgesic needs in labour.

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Author's reply

Dear Sir,

I thank Dr Cahill for his interest in my commentary. The benefits derived from one-to-one nursing with a sympathetic midwife are unarguable and one would hesitate to suggest subjecting such a form of management to a randomised control trial. Psychoprophylaxis I did not discuss because it was not a technique that was included in the Swedish survey (Gerdin & Cnattingius 1990). This technique *has* however been subjected to randomized trial (Freeman *et al.* 1986), which showed it did not improve the efficacy of analgesia but did prolong labour. Clearly however, it remains a valuable option in a hospital which is better staffed with keen protagonists of psychoprophylaxis than it is with trained obstetric anaesthetists.

Low epidural rates are not uncommon in a number of units in the UK as well as in Dublin. Although I am aware of the excellent atmosphere that pervades the National Maternity Hospital, nevertheless such low rates cannot be said necessarily to reflect high quality analgesia.

Critical readers may also notice that I did not address the subject of inhalational analgesia, the most widely used technique in labour. Those wanting a complete review of the subject would of course consult a text book or review article rather than a brief commentary.

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ADONIS 030654569100087J

Idiopathic thrombocytopenic purpura in pregnancy: A randomized trial on the effect of antenatal low dose corticosteroids on neonatal platelet count

Dear Sir

Having recently delivered a patient with the condition I was interested to read the report by Christiaens *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 893-898] on the failure of low dose maternal steroid therapy to prevent neonatal thrombocytopenia in cases of idiopathic thrombocytopenic purpura (ITP).

I was surprised that no mention was made of the reported presence of the IgG autoantibody in breast milk, particularly colostrum, and the adverse effects that this can have on the neonatal platelet count (Keleman *et al.* 1978). If any of the infants described were breast fed this could account for at least some of the infants with neonatal thrombocytopenia, clouding the issue of whether the proposed treatment was beneficial or not. It does appear from the figures presented that if infants with thrombocytopenia diagnosed only at birth are considered, there remains no statistically significant difference between the treated (1 severe and 5 mild) and untreated (1 severe and 4 mild) groups.

In view of the published evidence I would support the opinion of Katz & Duncan (1975), that lactation should usually be discouraged in mothers with ITP. The influence of breast feeding should be considered whenever the effects of any treatment on neonatal platelet counts are examined.

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References

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Authors' reply

Dear Sir,

Dr Roberts justly remarks that the presence of autoantibodies has been reported in colostrum. In our series nine infants were formula fed and 19 were breast fed. The median lowest neonatal platelet count in the first week of life was 120×10^9/l (range 17–275 × 10^9/l) in the formula fed group and 120×10^9/l (range 15–248 × 10^9/l) in the breast fed group. Since the proportions of splenectomized women were different in these groups the subgroups were tested separately and the results are shown in Figure 1.

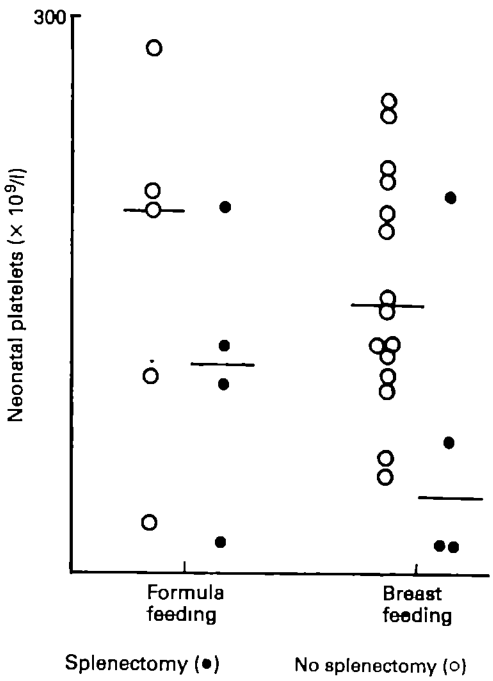

Fig. 1. Lowest neonatal platelet counts during the first week of life in four subgroups Individual counts and median for each group are shown

The lowest neonatal platelet counts during the first week of life were lower in the breast fed than in the formula fed infants in each subgroup but the differences were not significant (Kruskal Wallis test). Median lowest neonatal platelet counts were also lower in infants of splenectomized mothers than in infants of mothers without splenectomy ($P = 0{\cdot}06$ in the Mann-Whitney *U* test). The numbers are too small to allow us to test if the effect of breast feeding on neonatal platelet counts is greater in infants of splenectomized mothers than in those of women who still have their spleens.

Kelemen *et al.* (1978), referred to by Dr Roberts, did not demonstrate an adverse effect of breast feeding on neonatal platelet counts, but only drew attention to the fact that small quantities of maternal immunoglobulins can be resorbed through the colostrum. Other authors (Hanson 1982) have stated that humans take up no or insignificant quantities of early colostral antibodies. Finally, breast feeding did not worsen thrombocytopenia in an infant with severe neonatal thrombocytopenia due to maternal ITP (Meschengieser & Lazzari 1986). Consequently, we do not discourage women with idiopathic thrombocytopenic purpura from breast feeding their infants.

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ADONIS 030654569100088W

Early recurrent miscarriage: histology of conception products

Dear Sir,

We read with interest the article by Houwert-de Jong *et al.* [*Br J Obstet Gynaecol* (1990) **97,** 533–535]. The study concerned pregnancy losses up to 16 weeks from the beginning of the last menstrual period. We wondered about the description of a fetus with a omphalocele. The presence of herniation of the intestines into the umbilical cord is physiological in embryos of 5–12 weeks developmental age (7–14 weeks gestational age, Moore 1989). In early pregnancy the diagnosis omphalocele can be made only in relation to the developmental age, which was not mentioned in the article (Kalousek *et al.* 1984). Please could you give us the additional information.

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Author's reply

Dear Sir,

Dr van Lijnschoten asks for more details of the fetus with an omphalocele that we describe in our report.

This fetus had a gestational age of 14 weeks and its development was appropriate for this point in pregnancy. There were no signs of maceration. There was a large omphalocele; the defect in the abdominal wall was about 3 cm in diameter. So in this case the herniation of the intestines was not only into the umbilical cord.

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BOOK REVIEWS

Baillière's Clinical Obstetrics and Gynaecology International Practice & Research. Volume 4, No 1. Antenatal Care March 1990, edited by M. H. Hall. Baillière Tindall, London, Philadelphia, 1990. 233 pages with figures and tables, £22.50 single issue, £49.00 annual subscription.

There is widespread confidence that early and frequent antenatal care can detect and prevent mortality and morbidity in women and their babies. Statistics that show that those with better outcomes had more antenatal visits are sometimes quoted in support of this argument. Of course, it is very much more complicated than that. A wide range of clinical procedures, tests and advice are available in a variety of different settings. Some of these have been shown in clinical trials to be effective in improving outcomes for particular groups of pregnant women, and some have not. The problem is to achieve a service which can provide what is effective to those who are most likely to benefit.

This volume, Antenatal Care, edited by Hall, goes a long way towards conveying the complexity of antenatal care. Views of clinical knowledge about and approaches to prepregnancy care and advice, routine testing and prophylaxis, multiple pregnancy and medical complications in pregnancy are given by Jewell, Terry, Campbell and Maresh in chapters 1, 2, 7 and 8. These chapters will give a fresh perspective to practitioners in obstetrics and midwifery, and each author provides a wealth of references.

Antenatal care consists of more than clinical tests and therapies, and this volume emphasizes the importance of recognizing how social and psychological factors affect outcome both directly because of physical effects of poverty and stress, and indirectly through lack of access to care Chapters by Bryce on social and midwifery support (chapter 5), and by Hepburn on social problems (chapter 9) illustrate how radical alternatives to the classic pattern of antenatal care could improve outcomes of pregnancy.

In the UK, a fail safe approach to risk assessment has resulted in large numbers of women without problems receiving care in specialist centres. Hall emphasizes that this need not be the case in her chapter on identification of high and low risk (chapter 4). The optimum use of resources for antenatal care for women with pregnancy hypertension is also discussed by Rosenberg & Twaddle (chapter 6).

The international perspective in this book shows readers that the volume of antenatal care provided is high in the UK compared to other countries in Europe, and is very high compared to developing countries (Buekens, chapter 11). The problems of bringing basic antenatal surveillance to women in rural parts of developing countries with few resources for health care may even suggest some lessons for the appropriate use of resources in the NHS: Nylander & Adekunle (Chapter 10) point out that, in Nigeria, women referred to a university hospital for confirmation of the gestation of their pregnancy were referred back to their rural services if there was no other apparent problem.

The final chapter (Guthrie *et al* chapter 12) outlines information needs for clinical and administrative purposes, and discusses clinical audit. There are many aspects of antenatal care that could be addressed in audit meetings. In the wake of repeated criticism of antenatal care provision in official reports on the maternity services in Britain, this book provides a very useful beginning for anyone with an interest in achieving a better service.

M. Mugford

Drugs in Pregnancy and Lactation. Third edition by Gerald C. Briggs, Roger K. Freeman & Sumner J. Yaffe. Williams & Wilkins, Baltimore, 1990, 732 pages illustrated, £45.00.

This book is designed like a pharmacopoeia and contains individual monographs on more than 500 drugs listed in alphabetical order by their USP names. Each drug is assigned a risk category for use in pregnancy, A, B, C, D or X, the latter being considered absolutely contraindicated. In addition to the alphabetical monographs the book carries an appendix in which the drugs are listed as well as USP names.

The reader is not burdened by discussions of the mechanisms of teratogenesis. There is little mention of the part that drug metabolites are believed to play and of the various theories that have evolved concerning the interactions of enzymes, enzyme inducers, smoking etc, and of the species differences in drug breakdown that can explain differing susceptibilities to teratogens.

Each monograph provides a thorough review of the literature and represents a very large amount of work. There is however a problem with evidence relating to drug teratogenesis that requires emphasis. Most drugs in common usage are very weak teratogens and in the vast majority of cases the link between a drug and congenital anomalies is tenuous. Five types of evidence may be adduced in an effort to assess the risk benefit ratio of an individual drug, and all have their pitfalls.

1. Major drug surveys by their very size can throw up chance associations.
2. Case controlled retrospective surveys give no idea of the incidence of a problem and are also probably subject to a positive reporting bias when mothers' memories are put to the test.
3. Cohort prospective studies have to be enormous if they are to reveal any but the most gross of teratogenic effects.
4. Isolated case reports are not only worthless but positively dangerous in that they may drive patients into the arms of newer and untried drugs.
5. Animal studies can overcome many of these problems, but are often worthless because of crucial metabolic differences between species.

The main text of each monograph is headed 'Fetal Risk Summary' but within this the authors have been wise not to stick to a rigid format. For example, if a drug has been given principally during labour it is this aspect of its use that is emphasized and the possible teratogenic effect gets only a passing mention. Under anaesthetics I was surprised to find only lignocaine (lidocaine) listed with no more modern local anaesthetics and no general anaesthetics. Has concern over a possible danger of anaesthesia in early pregnancy and the presence of trace concentrations in the environment been solely a British preoccupation?

I was surprised to find eight separate barbiturates each with its own monograph, though I believe their use in the US has dropped as dramatically as it has in this country. Individual oral anticoagulants on the other hand are all grouped together under coumarins, but this monograph covers several pages and provides an excellent analysis of the available information related to their danger in pregnancy. Alcohol and marijuana each rate eleven pages and this is exceeded only by cocaine with sixteen pages. Surprisingly I could find no mention of tobacco, cigarettes or nicotine.

Following the fetal risk summary is a breast feeding summary which mentions, where available, information about the milk content of maternal drugs, milk/plasma ratios, etc. The authors are aware however, that a milk/plasma ratio gives little idea of the actual amount of drug to be found in the baby's plasma It should be emphasized that, for the vast majority of drugs, the dose that a baby can derive from mother's milk is tiny compared to that it acquires by placental transfer. Thus unless neonatal clearance of the drug is exceptionally slow or the drug is particularly toxic to the baby, the risk of breast feeding is minute compared to that in utero.

This is a rapidly developing field and this edition is the third since 1983. Many of the references, however, date from the 70s or even before when much of the important work in this field was carried out. Since the previous edition, monographs on cocaine, indomethacin, isotretinoin, valproic acid, antineoplastic agents and the vitamins have been extensively revised while new drugs have been added.

Quibbling aside, it is clear that this is an excellent reference book of a format that is ideal for the busy clinician.

Felicity Reynolds

Clinical IVF Forum. Current Views in Assisted Reproduction, edited by Philip L. Matson & Brian A. Lieberman. Manchester University Press, Manchester and New York 1990. 150 pages with figures and tables, £12.95.

The editors are to be commended on the swift production of this small book, based on a meeting on assisted reproduction held in Manchester in May 1990. The chapters cover the usual areas, starting with a partly historical look at the use of GnRH analogues in assisted reproduction, and then assessing the use of growth hormone in women who have responded poorly to gonadotrophin stimulation. A further two chapters on ovarian stimulation precede two chapters on pregnancy outcome. The next chapter, which makes the case for a flexible approach to assisted conception provides an interesting backcloth to recent results which support the replacement of no more than two embryos in women under 35 years. There follows chapters on varied subjects, including counselling, zona micro manipulation and then three chapters on the treatment of the male. As always with books like this, the chapters reflect the experience and recent work of the individual centres. The price is modest and, indeed, the book has become widely available from representatives of a major pharmaceutical company. It is certainly worth reading for those who have an interest in the clinical and laboratory aspects of *in vitro* fertilization.

A. A. Templeton

The Johns Hopkins Handbook of In Vitro Fertilization and Associated Reproduction Technologies, edited by Martin D. Damewood. Little Brown and Company, Boston, Toronto, London, 1990, 176 pages with figures and tables. £19.95.

This handbook describes IVF and related procedures as practised in the John Hopkins Hospital, where there has been an IVF programme for some considerable time. It represents, as the blurb says, state of the art technologies, and as such is probably destined to have a rather short shelf life. The sections include Screening, The Team, The Procedure, The Laboratory, Contemporary Procedures (i.e , GIFT and cryopreservation) and a curious section entitled Contemporary Considerations which includes both Ethics and Finance. Sadly, the last section does not take the opportunity of addressing the ethics of finance, but then it is not the purpose of this book to be provocative.

The book is put together as a handbook, and as such fulfils its function quite well. There is nothing particularly uplifting in any of the chapters, although the chapter on follicular maturation and monitoring is perhaps the best considered, and certainly the best referenced. The purpose of some chapters is unclear, particularly that on the morphology of oocytes. The chapter on cryopreservation is very limited and does not for example, address the interesting data from the US suggesting that zygotes survive freezing better than developed embryos.

I suppose my main objection to this type of book is the feeling that IVF is something that you can pick up a handbook and do. At a time when there is a serious need to scrutinize practice, licence clinics, and structure training, this seems inappropriate.

A. A. Templeton

Obstetrics (Colour Aids) by D. K. James & M. Pillai. Churchill Livingstone, Edinburgh, 1990, 145 pages, with figures and tables, £6.50

Zuzpan and Quilligan's Manual of Obstetrics and Gynecology. Second edition, edited by Jay D. Iams & Frederick P. Zuzpan. C. V. Mosby Co., St Louis, 1990, 442 pages, with figures and tables, £22.50

Manual of Clinical Problems in Obstetrics and Gynaecology. Third Edition by Michel E. Rivlin, John C. Morrison & G. William Bates. Little Brown & Company, Boston, Toronto, London, 460 pages, with figures and tables, £9.95

These three new books include two manuals and one small colour atlas that are aimed at different groups of readers.

The colour aids is pocket sized and intended for 'self study and refreshing knowledge'. It logically covers all aspects of obstetrics from antenatal care through labour and delivery to the puerperium and contraception, apart from placing antepartum haemorrhage between third stage problems and episiotomy repair.

Good quality photographic plates are used to illustrate the concise text, especially those on fetal congenital abnormalities. Some of the illustrations are a little simplistic—photographs of boxes of drugs—but there are some excellent series of photographs on practical procedures such as normal delivery, breech delivery and caesarean section.

I did not feel that this was a book that the market particularly required but, now published, I might suggest to undergraduates that they use it to illustrate textbook prose and that the photographs of practical procedures should be studied before spending time in the labour ward.

Zuzpan and Quilligan's Manual of Obstetrics and Gynaecology consists of 37 brief chapters by 25 contributors which extend the editors' first edition on obstetrics to include gynaeology. The editors state that the manual is intended to supply information to assist the clinician in arriving at a diagnosis by deductive reasoning. This has barely been achieved in the obstetric section but is marginally more successful in the gynaecological section.

The chapters vary in thoroughness; the standard should have been set by the excellent chapter on breastfeeding. The balance in the obstetric section is poor with less than one page on postpartum haemorrhage, whilst different types of maternal cardiac defects are given four pages. Deep venous thrombosis is not discussed in the medical problems section. One useful arrangement in the gynaecological section is 'what to look for/what to do' in vulvovaginitis and there is a good differential diagnosis of a pelvic mass. Each chapter ends with a few MCQs but, unfortunately, the style is not that which is usually found in UK examinations. One assumes that the manual is aimed at the practising clinician but I do not feel that it would be a wise use of £22.50, nor to any level of student.

Rivlin *et al's* book is the third edition of an American manual of obstetrics and gynaecology written by 35 contributors. All aspects of obstetrics and gynaecology are covered comprehensively. The sections on infectious diseases and human sexuality have been expanded. Each topic is concisely and authoritatively covered in two to three pages followed by two pages of up-to-date key references which have been annotated. This is an extremely useful reference manual and is an essential purchase for the MRCOG student, especially prior to writing the long case commentaries. I found that this manual assumes a level of understanding inappropriate to the undergraduate.

On a practical note, the paper is thin and the spiral binding almost too small for the 460 pages which I fear will tear if well read. The print is small and narrowly spaced and a magnifying glass might help certain readers.

Overall, I would recommend the purchase of the Rivlin manual which is good value for £9.95

Felicity Ashworth

The F.I.G.O Manual of Human Reproduction. Three Volumes.

Volume 1: Reproduction Physiology edited by Luigi Mastrianni Jr & Christos Coutifaris. 150 pages, with figures and tables

Volume 2: Family Planning edited by M. F. Fathalla, A. Rosenfield & C. Indriso, 220 pages

Volume 3: Reproductive Health. Global Issues edited by M. F. Fathalla, A. Rosenfield, C. Indriso, D. K. Sen & S. S. Ratnam. 250 pages, Parthenon Publishing Group, Carnforth, Lancs, 1990, £19 per volume or £49 per set

The Figo Manual of Human Reproduction provides in three volumes a comprehensive, up-to-date and authoritative information package backed by pertinent debate about issues of global importance. I was particularly impressed by the worldwide approach which runs as a thread through all three volumes and keeps the reader from the dangers of being too academic or parochial, whilst at the same time providing necessary knowledge in an easily readable and understood form.

I was disappointed that sexual behaviour and dysfunction were not covered as a specific topic. However, I still heartily recommend the whole manual and believe it should be available to students and postgraduates in all obstetric and gynaecology departments, GP vocational training schemes and community health and public health departments.

The three volumes can be purchased together as a boxed set for £49 or individually for £19. The typical format is for the text to cover half the page, with relevant photographs, illustrations, graphs or key phrases alongside. I found this helpful but, in this age of conservation, I was concerned by the waste of paper, as many pages contain large areas that are blank. This somehow devalued the global concerns dealt with in the text.

The illustrations are also available as slides. There are 550 slides altogether at a cost of £250 for the set of three or £95 for the set belonging to each volume. The slides can be used for teaching purposes. When the slides are ordered the relevant volume is sent free.

Volume 1, 'Reproductive Physiology', has six chapters that cover anatomy, physiology, endocrinology, embryology and genetics relating to human reproduction. The text is clear and concise and backed up by illustrations that help to clarify some difficult concepts.

Volume 2, 'Family Planning', has nine chapters and, apart from comprehensively reviewing each method, also considers pregnancy termination and reviews family planning programmes and services worldwide.

Volume 3, 'Reproductive Health. Global Issues', was for me the most exciting of the volumes. There are 10 chapters, each tackling emotive and internationally important topics relevant to the whole of mankind.

The volume starts with a review of the social aspects of reproductive health and moves onto a chapter that deals with world population, population predictions and their relevance. Contraception is then tackled from the point of view of current technology, safety and acceptability. There follow chapters on infertility, maternal mortality, adolescent sexuality and pregnancy, and sexually transmitted diseases. HIV infection is covered especially from the point of view of women and children. Gynaecological and breast cancer screening and early diagnosis are reviewed and the current problems and controversies well discussed. The volume ends with a chapter emphasizing the importance, globally, of breast feeding.

Fran Reader

Female Urinary Incontinence (Proceedings of an Educational Course held at the Royal College of Obstetricians and Gynaecologists, June 1989) edited by R. J. Jarvis. Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG. 1990. 89 pages with figures and tables, £6.00 (available from the above address)

This is a truly remarkable book. It is short (89 pages), but it manages to cover all the important issues of female incontinence which most gynaecologists are likely to encounter. Yet it does so with a lightness of touch and a lack of dogma, and manages to remain easily readable, never falling into the trap of telegraphic style. The editor, who contributed four of the twelve chapters, and the RCOG are to be congratulated. I can think of no practising gynaecologist at any level (apart from experts in gynaecological urology) who will not benefit from buying this book, and at £6 there really is no excuse for hesitating.

Richard Porter

The Immunology of the Fetus edited by Gérard Chaouat. CRC Press, Boca Raton, Florida, 1990. 320 pages with figures and tables, $120

The caption to figure 8 on page 277 of this book reads: 'Genetic drift in the nursery. Pony mares with their surrogate, extraspecies donkey, Przewalski's horse and Grant's zebra foals resulting from embryo transfer'. This admirably summarizes the virtues and defects of this capricious, often zany compilation. One imagines that most obstetricians or scientists attracted by the title of this book will be seeking an informed, clear synthesis of current views on the survival of the fetus in its seemingly hostile immunological environment. Furthermore, the subject has wider implications for disorders in pregnancy and, indeed other contexts. Given the flood of new data relating to the conflicting theories in this area, judicious and informed opinion is at least as more important as factual recitation. In the event one is offered a potpourri of essays variably related to the book's presumed theme. Some contributions deal very ably with the survival of the fetal homogaft, notably those by Webb & Johnson on trophoblastic antigenicity, Billington on the maternal immune recognition of the fetus and Wegmann on immune stimulation of placental growth. Other offerings are either controversial, for example those dealing with recurrent abortion, or too basic for a book of this kind, for example the description of the development of the T cell repertoire. Again, if one is going to include any congenital disorders, it is rather arbitrary to discuss immunodeficiency diseases simply because they have a loose affinity with the title.

The quixotic choice of subjects for inclusion is accentuated by the anarchic range of styles. Some contributions are research communications packed with fine detail while others, more appropriately, are essays with selective experimental validation. The most fitting title is the 'brief overview on the major histocompatibility complex' which is indeed telegraphic to near vanishing point. Most of the references end in 1987; does this mean that the manuscripts were premature or that the book is post-mature? This loose compilation with well nigh invisible editorial control is all right for selective browsing but it is not a guide to this field for acolytes or cognoscenti.

A. M. Denman

Postreproductive Gynecology edited by Hugh M. Shingleton & W. Glenn Hurt. Churchill Livingstone, New York, Edinburgh, London, 1990. 528 pages, 120 illustrations, £60

This is an uncommon approach to a common set of problems. There are many gynaecological complaints which afflict women over 40 years and to collect them into a symposium, as it were, and give an 'overview' is a sensible if unusual way of dealing with these special areas of gynaecology. The book stems from Alabama, Virginia and Michigan and has a traditional American approach but, as such, is a useful reference book and should find a place in British libraries.

The opening chapter reviews the biology of ageing. This process, which affects all living organisms, must be understood by gynaecologists, who need to know the differences in physiology between men and women. There is a useful comment on life-style and longevity at the end of this chapter, which we would all benefit from reading. Perhaps the most telling comment is on the regimented life-style shown to be effective in maintaining health but which, the authors concede, may detract from the enjoyment of living.

Most of the gynaecological conditions that are commonly encountered in this age group are reviewed. Hormone replacement therapy, abnormal uterine bleeding, pelvic masses, prolapse, and so on, are discussed. But a wider approach is adopted by considering chronic medical conditions, breast diseases and acute medical and surgical complications.

Reading an American textbook inevitably leads to areas of disagreement from the United Kingdom. Do we really need to include salpingo oophorectomy in our vaginal hysterectomies, for instance, and do we need to follow the exhaustive list of sometimes expensive tests for abnormal perimenopausal bleeding? The benefit of a different approach, however, is to concentrate the mind more on our own methods and to review them critically.

As a text for reference this book has a refreshing approach and provides some interesting and light relief for the postgraduate student.

Mary Anderson

Books received some of which may be reviewed at a later date

The Management of Infertility by John Yovich and Gedis Grudzinskas. Heinemann Medical Books, Oxford, 1990, 276 pages fully illustrated £45.00

Physiotherapy in Obstetrics and Gynaecology by Margaret Polden & Jill Mantle. Butterworth Heinemann, Oxford, London, 1990, 441 pages, illustrated £29.95

Baillière's Clinical Obstetrics and Gynaecology Computing and Decision Support in Obstetric and Gynaecology Volume 4 Number 4, December 1990 edited by R. J. Lilford. Baillière Tindall, London, Philadelphia, 1990, pages 655–914, illustrated, Annual subscription $49.00 for UK. Single issue £22.50

The NO-Hysterectomy Option. Your Body—Your Choice by Herbert A Goldfarb with Judith Greif. John Wiley & Sons, Inc New York, Chichester, 1990, 265 pages, illustrated, £20.65

The Principles and Practice of Ultrasonography in Obstetrics and Gynecology Fourth edition edited by A. C. Fleischer, R. Romero, F. Manning, P. Jeanty and A. Everette James. Prentice-Hall International Inc., 1990, 668 pages fully illustrated with colour plates, £62.00

Medical Statistics on Microcomputers by R. A. Brown & J. Swanson Beck, British Medical Journal, London, 1990, 103 pages with figures and tables £8.95

Science and Babies. Private Decisions, Public Dilemmas by Suzanne Wymelenberg for the Institute of Medicine. National Academy Press, Washington, 1990, 174 pages, hardback £14.25, paperback £7.10

Effective Choices for Diagnostic Imaging in Clinical Practice Report of a WHO Scientific Group. Technical Report Series No 795, World Health Organization, Geneva 1990, 131 pages Sw fr. 18./US $14.40

Proceedings and Symposiums

HRT and Osteoporosis edited by J. O. Drife & J. W. W. Studd. Report of the 22nd Study Group held at the Royal College of Obstetricians and Gynaecologists in January 1990 Springer-Verlag, London, Berlin, Heidelberg, 394 pages with 65 figures £60.00

Micturition edited by J. O. Drife, P. Hilton & S. L. Stanton. Report of the 21st Study Group held at the Royal College of Obstetricians and Gynaecologists in October 1989. Springer-Verlag, London, Berlin, Heidelberg, 1990 356 pages, with 101 figures, £65.00

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